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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	5	MAR 02	GBFULL: New full-text patent database on STN
NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	20	JUN 13	RUSSIAPAT: New full-text patent database on STN
NEWS	21	JUN 13	FRFULL enhanced with patent drawing images
NEWS	22	JUN 27	MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS	23	JUL 01	MEDICONF removed from STN
NEWS	24	JUL 07	STN Patent Forums to be held in July 2005
NEWS	25	JUL 13	SCISEARCH reloaded
NEWS	26	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available
NEWS	27	AUG 11	Derwent World Patents Index(R) web-based training during August
NEWS	28	AUG 11	STN AnaVist workshops to be held in North America

NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items

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 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005

=> file registry
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   22 AUG 2005  HIGHEST RN 861291-85-2
DICTIONARY FILE UPDATES:  22 AUG 2005  HIGHEST RN 861291-85-2

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> E "PEG"/CN 25
E1            1     PEFURAZOATE/CN
E2            1     PEFURAZOATE-IKI 220 MIXT./CN
E3            1 --> PEG/CN
E4            1     PEG (POLYGLYCOL)/CN
E5            1     PEG 100/CN
E6            1     PEG 1000/CN
```

```
E7            1     PEG 1000 DIAMINE/CN
E8            1     PEG 1000 MONOSTEARATE/CN
E9            1     PEG 10000/CN
E10           1     PEG 1000MO/CN
E11           1     PEG 1000MS/CN
E12           1     PEG 100MS/CN
E13           1     PEG 11000/CN
E14           1     PEG 115/CN
E15           1     PEG 120 METHYL GLUCOSE DIOLEATE/CN
E16           1     PEG 120 METHYL GLUCOSE TRIOLEATE/CN
E17           1     PEG 12000/CN
E18           1     PEG 13000/CN
E19           1     PEG 1450/CN
E20           1     PEG 150 STEARATE/CN
E21           1     PEG 1500/CN
E22           1     PEG 1500-1,5-PENTANEDIOL-TEREPHTHALIC ACID-TRIMETHYLOLPROPANE
COPOLYMER ESTER WITH DODECENYLSUCCINIC ANHYDRIDE/CN
E23           1     PEG 1500-1,5-PENTANEDIOL-TEREPHTHLAIC ACID-TRIMETHYLOLPROPANE
COPOLYMER ESTER WITH DODECENYLPHTHALIC ANHYDRIDE/CN
E24           1     PEG 1500-1,5-PENTANEDIOL-TEREPHTHLAIC ACID-TRIMETHYLOLPROPANE
COPOLYMER ESTER WITH PHTHALIC ANHYDRIDE/CN
E25           1     PEG 15000/CN

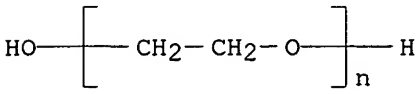
=> S E3
L1            1 PEG/CN

=> DIS L1 1 SQIDE
THE ESTIMATED COST FOR THIS REQUEST IS 6.15 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   25322-68-3  REGISTRY
CN   Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   α,ω-Hydroxypoly(ethylene oxide)
CN   α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)
CN   α-Hydro-ω-hydroxypoly(oxyethylene)
CN   1,2-Ethanediol, homopolymer
CN   1660O
CN   1660S
CN   400DAB8
CN   Alkox
CN   Alkox E 100
CN   Alkox E 130
CN   Alkox E 160
CN   Alkox E 240
CN   Alkox E 30
CN   Alkox E 30G
CN   Alkox E 45
CN   Alkox E 60
CN   Alkox E 75
CN   Alkox R 100
CN   Alkox R 1000
CN   Alkox R 15
CN   Alkox R 150
CN   Alkox R 400
CN   Alkox SR
CN   Alkox SW
CN   Antarox E 4000
CN   Aquacide III
CN   Aquaffin
CN   Badimol
```

CN BDH 301
CN Bradsyn PEG
CN Breox 2000
CN Breox 20M
CN Breox 4000
CN Breox 550
CN Breox PEG 300
CN CAFO 154
CN Carbowax
CN Carbowax 100
CN Carbowax 1000
CN Carbowax 1350
CN Carbowax 14000
CN Carbowax 1450
CN Carbowax 1500
CN Carbowax 1540
CN Carbowax 20
CN Carbowax 200
CN Carbowax 20000
CN Carbowax 25000
CN Carbowax 300
CN Carbowax 3350
CN **PEG**
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
AR 9002-90-8
DR 615575-04-7, 12676-74-3, 12770-93-3, 9081-95-2, 9085-02-3, 9085-03-4, 174460-08-3, 174460-09-4, 54510-95-1, 125223-68-9, 54847-64-2, 59763-40-5, 64441-68-5, 64640-28-4, 133573-31-6, 25104-58-9, 25609-81-8, 134919-43-0, 101677-86-5, 99264-61-6, 106186-24-7, 112895-21-3, 114323-93-2, 50809-04-6, 50809-59-1, 119219-06-6, 60894-12-4, 61840-14-0, 37361-15-2, 112384-37-9, 67411-64-7, 70926-57-7, 75285-02-8, 75285-03-9, 77986-38-0, 150872-82-5, 154394-38-4, 79964-26-4, 80341-53-3, 85399-22-0, 85945-29-5, 90597-70-9, 88077-80-9, 88747-22-2, 34802-42-1, 107502-63-6, 107529-96-4, 116549-90-7, 156948-19-5, 169046-53-1, 188364-77-4, 188924-03-0, 189154-62-9, 191743-71-2, 196696-84-1, 201163-43-1, 206357-86-0, 221638-71-7, 225502-44-3, 270910-26-4, 307928-07-0, 356055-70-4, 391229-98-4
MF (C2 H4 O)n H2 O
CI PMS, COM
PCT Polyether
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SCISEARCH, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Preprint; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

84039 REFERENCES IN FILE CA (1907 TO DATE)
22615 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
84192 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.87	7.08

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005

FILE LAST UPDATED: 20 AUG 2005 (20050820/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l1
L2 185 L1

=> s PEG
9298 PEG
747 PEGS
L3 9685 PEG
(PEG OR PEGS)

=> s poly () ethylene () glycol
59257 POLY
6 POLIES
59263 POLY

```
                (POLY OR POLIES)
          18961 ETHYLENE
           2287 ETHYLENES
          19618 ETHYLENE
                (ETHYLENE OR ETHYLENES)
          22544 GLYCOL
          27720 GLYCOLS
          40275 GLYCOL
                (GLYCOL OR GLYCOLS)
L4         2487 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol
             66 METHOXYPOLY
          18961 ETHYLENE
           2287 ETHYLENES
          19618 ETHYLENE
                (ETHYLENE OR ETHYLENES)
          22544 GLYCOL
          27720 GLYCOLS
          40275 GLYCOL
                (GLYCOL OR GLYCOLS)
           8421 ETHYLENE GLYCOL
                (ETHYLENE(W)GLYCOL)
L5           52 METHOXYPOLY (W) ETHYLENE GLYCOL

=> s l5 or l4 or l3
L6        10866 L5 OR L4 OR L3

=> s antibod?
L7       694206 ANTIBOD?

=> s clearance or clear or excret? or removed or removal
          89107 CLEARANCE
           5664 CLEARANCES
          91341 CLEARANCE
                (CLEARANCE OR CLEARANCES)
         128624 CLEAR
            549 CLEARS
         129145 CLEAR
                (CLEAR OR CLEARS)
         116634 EXCRET?
          99889 REMOVED
         142890 REMOVAL
           1080 REMOVALS
         143364 REMOVAL
                (REMOVAL OR REMOVALS)
L8       538410 CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

=> s l8 and l6
L9         1041 L8 AND L6

=> s l9 and l7
L10         129 L9 AND L7

=> s anti-PEG
         574125 ANTI
              6 ANTIS
         574129 ANTI
                (ANTI OR ANTIS)
           9298 PEG
            747 PEGS
           9685 PEG
                (PEG OR PEGS)
```

```
L11          7 ANTI-PEG
                 (ANTI(W)PEG)

=> s l11 and l8
L12          2 L11 AND L8

=> d ibib 1-2

L12  ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:    2002229521     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 11966757
TITLE:               The in vivo effects of tumour necrosis factor blockade on
                     the early cell mediated immune events and syndrome
                     expression in rat adjuvant arthritis.
AUTHOR:              Bush K A; Kirkham B W; Walker J S
CORPORATE SOURCE:    School of Physiology & Pharmacology, University of New
                     South Wales, NSW, Australia.
SOURCE:              Clinical and experimental immunology, (2002 Mar) 127 (3)
                     423-9.
                     Journal code: 0057202. ISSN: 0009-9104.
PUB. COUNTRY:        England: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200209
ENTRY DATE:          Entered STN: 20020423
                     Last Updated on STN: 20020906
                     Entered Medline: 20020904

L12  ANSWER 2 OF 2     MEDLINE on STN
ACCESSION NUMBER:    2000191525     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 10725103
TITLE:               Efficient clearance of poly(ethylene
                     glycol)-modified immunoenzyme with anti-
                     PEG monoclonal antibody for prodrug cancer therapy.
AUTHOR:              Cheng T L; Chen B M; Chern J W; Wu M F; Roffler S R
CORPORATE SOURCE:    Institute of Biomedical Sciences, Academia Sinica, Taipei,
                     Taiwan.
SOURCE:              Bioconjugate chemistry, (2000 Mar-Apr) 11 (2) 258-66.
                     Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200005
ENTRY DATE:          Entered STN: 20000613
                     Last Updated on STN: 20000613
                     Entered Medline: 20000531


=> d his

     (FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
               E "PEG"/CN 25
L1             1 S E3

     FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2           185 S L1
L3          9685 S PEG
L4          2487 S POLY () ETHYLENE () GLYCOL
L5            52 S METHOXYPOLY () ETHYLENE GLYCOL
```

```
L6         10866 S L5 OR L4 OR L3
L7        694206 S ANTIBOD?
L8        538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9          1041 S L8 AND L6
L10          129 S L9 AND L7
L11            7 S ANTI-PEG
L12            2 S L11 AND L8

=> s l11 not py>1999
       3085459 PY>1999
L13            3 L11 NOT PY>1999

=> d ibib 1-3

L13  ANSWER 1 OF 3     MEDLINE on STN
ACCESSION NUMBER:    1998089627     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 9428158
TITLE:               Immobilization of L-asparaginase into a biocompatible
                     poly(ethylene glycol)-albumin hydrogel: evaluation of
                     performance in vivo.
AUTHOR:              Jean-Francois J; D'Urso E M; Fortier G
CORPORATE SOURCE:    Departement de Chimie-Biochimie, Universite du Quebec,
                     Montreal, Canada.
SOURCE:              Biotechnology and applied biochemistry, (1997 Dec) 26 ( Pt
                     3) 203-12.
                     Journal code: 8609465. ISSN: 0885-4513.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199802
ENTRY DATE:          Entered STN: 19980217
                     Last Updated on STN: 20000303
                     Entered Medline: 19980205

L13  ANSWER 2 OF 3     MEDLINE on STN
ACCESSION NUMBER:    84160696     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 6706424
TITLE:               Polyethylene glycol reactive antibodies in man: titer
                     distribution in allergic patients treated with monomethoxy
                     polyethylene glycol modified allergens or placebo, and in
                     healthy blood donors.
AUTHOR:              Richter A W; Akerblom E
SOURCE:              International archives of allergy and applied immunology,
                     (1984) 74 (1) 36-9.
                     Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY:        Switzerland
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         198405
ENTRY DATE:          Entered STN: 19900319
                     Last Updated on STN: 19970203
                     Entered Medline: 19840522

L13  ANSWER 3 OF 3     MEDLINE on STN
ACCESSION NUMBER:    83107741     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 6401699
TITLE:               Antibodies against polyethylene glycol produced in animals
                     by immunization with monomethoxy polyethylene glycol
                     modified proteins.
AUTHOR:              Richter A W; Akerblom E
SOURCE:              International archives of allergy and applied immunology,
```

(1983) 70 (2) 124-31.
Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198303
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830311

=> d kwic 1

L13 ANSWER 1 OF 3 MEDLINE on STN
AB . . . spleen or liver. ELISA tests at 28 days and 120 days showed the presence of anti-ASNase (and, in lower amounts, **anti-PEG**) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of fibroblast-like cell. . .

=> d kwic 2

L13 ANSWER 2 OF 3 MEDLINE on STN
AB . . . allergies and in healthy blood donors employing passive hemagglutination. In untreated allergic patients and in healthy blood donors, naturally occurring **anti-PEG** antibody titers between 32 and 512 were seen in 3.3 and 0.2%, respectively. During hyposensitization with monomethoxy polyethylene glycol modified ragweed extract and honey bee venom, respectively, the patients showed an **anti-PEG** antibody response. Titers of 32-512 were found in 50% of the patients directly after the first treatment course. After 2. . . years of treatment the percentage of patients with such titers declined to 28.5%. Mercaptoethanol treatment of sera indicated that the **anti-PEG** antibodies predominantly were of the IgM isotype. The weak IgM response found in treated patients is considered to be of. . .

=> d kwic 3

L13 ANSWER 3 OF 3 MEDLINE on STN
AB . . . protein and the degree of modification. With modified OA, in the presence of FCA, the majority of animals showed an **anti-PEG** response. With modified SOD and Rag only a small proportion of animals responded. In the absence of FCA, modified OA, given s.c., did not elicit any **anti-PEG** antibody response in rabbits and only a weak response in mice. PEG of MW 10,000 and 100,000 given in FCA. . . mice, showed no or very poor immunogenic properties. Gel diffusion, heterologous passive anaphylaxis and passive hemagglutination were used to demonstrate **anti-PEG** antibodies raised to PEG-modified proteins. Specificity was confirmed by hapten inhibition of precipitation, inhibition of passive hemagglutination and cross-reactivity tests.. . . by PEG of MW 300 it appears that the antigenic determinant of PEG may be a sequence of 6-7 -CH2CH2O-units. **Anti-PEG** antibodies can be used analytically. By gel diffusion, Peg was detected in minimal concentrations of 0.1-1 microgram/ml. The clinical relevance. . .

=> d ab 3

L13 ANSWER 3 OF 3 MEDLINE on STN
AB Antibodies to polyethylene glycol (PEG) were raised in rabbits by immunization with monomethoxy polyethylene glycol modified ovalbumin (OA), bovine superoxide dismutase (SOD), and ragweed pollen extract (Rag), given in Freund's complete adjuvant (FCA). Immunogenicity depended on the nature of the protein and the degree of modification. With modified OA, in the presence of FCA, the majority of animals showed an **anti-PEG** response. With modified SOD and Rag only a small proportion of animals responded. In the absence of FCA, modified OA, given s.c., did not elicit any **anti-PEG** antibody response in rabbits and only a weak response in mice. PEG of MW 10,000 and 100,000 given in FCA was found nonimmunogenic in rabbits, and PEG of MW 5.9 X 10(6), given s.c. to mice, showed no or very poor immunogenic properties. Gel diffusion, heterologous passive anaphylaxis and passive hemagglutination were used to demonstrate **anti-PEG** antibodies raised to PEG-modified proteins. Specificity was confirmed by hapten inhibition of precipitation, inhibition of passive hemagglutination and cross-reactivity tests. PEG of MW greater than or equal to 4,000 produced specific precipitates, smaller molecules acted as monovalent haptens. From hapten inhibition of precipitation by PEG of MW 300 it appears that the antigenic determinant of PEG may be a sequence of 6-7 -CH2CH2O-units. **Anti-PEG** antibodies can be used analytically. By gel diffusion, Peg was detected in minimal concentrations of 0.1-1 microgram/ml. The clinical relevance of these findings with regard to therapy with PEG-modified enzymes and allergens in humans remains to be established.

=> d kwic

L13 ANSWER 1 OF 3 MEDLINE on STN
AB . . . spleen or liver. ELISA tests at 28 days and 120 days showed the presence of anti-ASNase (and, in lower amounts, **anti-PEG**) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of fibroblast-like cell. . .

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
E "PEG"/CN 25
L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2 185 S L1
L3 9685 S PEG
L4 2487 S POLY () ETHYLENE () GLYCOL
L5 52 S METHOXYPOLY () ETHYLENE GLYCOL
L6 10866 S L5 OR L4 OR L3
L7 694206 S ANTIBOD?
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9 1041 S L8 AND L6
L10 129 S L9 AND L7
L11 7 S ANTI-PEG
L12 2 S L11 AND L8
L13 3 S L11 NOT PY>1999

=> s l10 not py>1999
3085459 PY>1999
L14 97 L10 NOT PY>1999

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=> s l14 not py>1998
       3546810 PY>1998
L15          90 L14 NOT PY>1998

=> s increase? or accelerat?
       1841898 INCREASE?
         88142 ACCELERAT?
L16    1898836 INCREASE? OR ACCELERAT?

=> s l16 and l15
L17          24 L16 AND L15

=> s l16 (S) l8
L18       51664 L16 (S) L8

=> s l18 and l17
L19           7 L18 AND L17

=> d ibib 1-4

L19  ANSWER 1 OF 7     MEDLINE on STN
ACCESSION NUMBER:   1998151177     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 9492213
TITLE:              Improved local delivery of TGF-beta2 by binding to
                    injectable fibrillar collagen via difunctional polyethylene
                    glycol.
AUTHOR:             Bentz H; Schroeder J A; Estridge T D
CORPORATE SOURCE:   Research and Development, Collagen Corporation, Palo Alto,
                    California 94303, USA.
SOURCE:             Journal of biomedical materials research, (1998 Mar 15) 39
                    (4) 539-48.
                    Journal code: 0112726. ISSN: 0021-9304.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199804
ENTRY DATE:         Entered STN: 19980422
                    Last Updated on STN: 19980422
                    Entered Medline: 19980413

L19  ANSWER 2 OF 7     MEDLINE on STN
ACCESSION NUMBER:   97415461     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 9271260
TITLE:              Immunogenicity and pharmacokinetic attributes of
                    poly(ethylene glycol)-grafted
                    immunoliposomes.
AUTHOR:             Harding J A; Engbers C M; Newman M S; Goldstein N I;
                    Zalipsky S
CORPORATE SOURCE:   SEQUUS Pharmaceuticals, Incorporated, Menlo Park, CA 94025,
                    USA.
SOURCE:             Biochimica et biophysica acta, (1997 Jul 25) 1327 (2)
                    181-92.
                    Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY:       Netherlands
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199709
ENTRY DATE:         Entered STN: 19970926
                    Last Updated on STN: 20000303
                    Entered Medline: 19970918
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L19 ANSWER 3 OF 7 MEDLINE on STN
ACCESSION NUMBER: 95071855 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7981064
TITLE: The potential for enhanced tumour localisation by **poly(ethylene glycol)** modification of anti-CEA **antibody**.
AUTHOR: Pedley R B; Boden J A; Boden R; Begent R H; Turner A; Haines A M; King D J
CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School of Medicine, London, U.K.
SOURCE: British journal of cancer, (1994 Dec) 70 (6) 1126-30. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950116
Last Updated on STN: 19980206
Entered Medline: 19950103

L19 ANSWER 4 OF 7 MEDLINE on STN
ACCESSION NUMBER: 92235285 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1569204
TITLE: IgG **antibody** response to polyethylene glycol-modified adenosine deaminase in patients with adenosine deaminase deficiency.
AUTHOR: Chaffee S; Mary A; Stiehm E R; Girault D; Fischer A; Hershfield M S
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710.
CONTRACT NUMBER: DK20902 (NIDDK)
SOURCE: Journal of clinical investigation, (1992 May) 89 (5) 1643-51. Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920612
Last Updated on STN: 19920612
Entered Medline: 19920526

=> d kwic 3

L19 ANSWER 3 OF 7 MEDLINE on STN
TI The potential for enhanced tumour localisation by **poly(ethylene glycol)** modification of anti-CEA **antibody**.
AB Attachment of **poly(ethylene glycol)** (**PEG**) to proteins can greatly alter their pharmacological properties, including extending the plasma half-life and reducing immunogenicity, both of which are potentially beneficial to tumour targeting. IgG, F(ab')2 and Fab' fragments of the anti-CEA **antibody** A5B7 were chemically modified with **PEG** (M(r) 5,000), labelled with 125I and their pharmacokinetics compared with the unmodified forms in the LS174T colonic xenograft in nude mice. **PEG** modification of the intact **antibody** had little effect on biodistribution, although tumour localisation was slightly reduced. In contrast, similar modification of F(ab')2 and Fab'A5B7 significantly prolonged plasma half-life and **increased**

radioantibody accumulation in the tumour and to a lesser extent in normal tissues, but reduced tissue to blood ratios. Prior to modification, Fab' A5B7 (M(r) 50,000) cleared more rapidly from the circulation than F(ab')2 (M(r) 100,000), but after **PEG** attachment their biodistributions converged, while the tumour to blood ratios were reduced and resembled that of the intact **antibody**. The enhanced tumour accumulation, reduced normal tissue to blood ratios and potentially reduced immunogenicity of fragments after **PEG** attachment may therefore prove superior to either unmodified fragments or intact **antibody** for **antibody**-targeted therapy, although the **increased** plasma half-life may necessitate the use of a **clearance** mechanism.

CT Check Tags: In Vitro
*Adenocarcinoma: IM, immunology
Animals
Antibodies, Monoclonal: CH, chemistry
***Antibodies, Monoclonal: ME, metabolism**
*Carcinoembryonic Antigen: IM, immunology
*Colonic Neoplasms: IM, immunology
Humans
Immunoglobulins, Fab: ME, metabolism
Mice
Mice, Nude
Neoplasm. . .

CN 0 (**Antibodies**, Monoclonal); 0 (Carcinoembryonic Antigen); 0 (Immunoglobulins, Fab); 0 (Polyethylene Glycols)

=> d kwic ibib 3

L19 ANSWER 3 OF 7 MEDLINE on STN

TI The potential for enhanced tumour localisation by **poly(ethylene glycol)** modification of anti-CEA **antibody**.

AB Attachment of **poly(ethylene glycol)** (**PEG**) to proteins can greatly alter their pharmacological properties, including extending the plasma half-life and reducing immunogenicity, both of which are potentially beneficial to tumour targeting. IgG, F(ab')2 and Fab' fragments of the anti-CEA **antibody** A5B7 were chemically modified with **PEG** (M(r) 5,000), labelled with 125I and their pharmacokinetics compared with the unmodified forms in the LS174T colonic xenograft in nude mice. **PEG** modification of the intact **antibody** had little effect on biodistribution, although tumour localisation was slightly reduced. In contrast, similar modification of F(ab')2 and Fab'A5B7 significantly prolonged plasma half-life and **increased** radioantibody accumulation in the tumour and to a lesser extent in normal tissues, but reduced tissue to blood ratios. Prior to modification, Fab' A5B7 (M(r) 50,000) cleared more rapidly from the circulation than F(ab')2 (M(r) 100,000), but after **PEG** attachment their biodistributions converged, while the tumour to blood ratios were reduced and resembled that of the intact **antibody**. The enhanced tumour accumulation, reduced normal tissue to blood ratios and potentially reduced immunogenicity of fragments after **PEG** attachment may therefore prove superior to either unmodified fragments or intact **antibody** for **antibody**-targeted therapy, although the **increased** plasma half-life may necessitate the use of a **clearance** mechanism.

CT Check Tags: In Vitro
*Adenocarcinoma: IM, immunology
Animals
Antibodies, Monoclonal: CH, chemistry
***Antibodies, Monoclonal: ME, metabolism**

*Carcinoembryonic Antigen: IM, immunology
*Colonic Neoplasms: IM, immunology
Humans
Immunoglobulins, Fab: ME, metabolism
Mice
Mice, Nude
Neoplasm. . .
CN 0 (**Antibodies**, Monoclonal); 0 (Carcinoembryonic Antigen); 0 (Immunoglobulins, Fab); 0 (Polyethylene Glycols)
ACCESSION NUMBER: 95071855 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7981064
TITLE: The potential for enhanced tumour localisation by **poly(ethylene glycol)** modification of anti-CEA **antibody**.
AUTHOR: Pedley R B; Boden J A; Boden R; Begent R H; Turner A; Haines A M; King D J
CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School of Medicine, London, U.K.
SOURCE: British journal of cancer, (1994 Dec) 70 (6) 1126-30. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950116
Last Updated on STN: 19980206
Entered Medline: 19950103

=> d his

(FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
E "PEG"/CN 25
L1 1 S E3

FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2 185 S L1
L3 9685 S PEG
L4 2487 S POLY () ETHYLENE () GLYCOL
L5 52 S METHOXYPOLY () ETHYLENE GLYCOL
L6 10866 S L5 OR L4 OR L3
L7 694206 S ANTIBOD?
L8 538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9 1041 S L8 AND L6
L10 129 S L9 AND L7
L11 7 S ANTI-PEG
L12 2 S L11 AND L8
L13 3 S L11 NOT PY>1999
L14 97 S L10 NOT PY>1999
L15 90 S L14 NOT PY>1998
L16 1898836 S INCREASE? OR ACCELERAT?
L17 24 S L16 AND L15
L18 51664 S L16 (S) L8
L19 7 S L18 AND L17

=> d ibib 5-7

L19 ANSWER 5 OF 7 MEDLINE on STN
ACCESSION NUMBER: 91334430 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1714590

TITLE: Use of site-directed mutagenesis to enhance the epitope-shielding effect of covalent modification of proteins with polyethylene glycol.
AUTHOR: Hershfield M S; Chaffee S; Koro-Johnson L; Mary A; Smith A A; Short S A
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, NC 27710.
CONTRACT NUMBER: DK20902 (NIDDK)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1991 Aug 15) 88 (16) 7185-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M60917; GENBANK-M66858; GENBANK-M66859; GENBANK-M66860; GENBANK-M66861; GENBANK-M66862; GENBANK-S45955; GENBANK-S45957; GENBANK-S45959; GENBANK-S49265
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911006
Last Updated on STN: 19960129
Entered Medline: 19910918

L19 ANSWER 6 OF 7 MEDLINE on STN
ACCESSION NUMBER: 89391643 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2789501
TITLE: Low avidity **antibodies** to double stranded DNA in systemic lupus erythematosus: a longitudinal study of their clinical significance.
AUTHOR: Nossent J C; Huysen V; Smeenk R J; Swaak A J
CORPORATE SOURCE: Department of Rheumatology, Dr Daniel den Hoed Clinic, Rotterdam, The Netherlands.
SOURCE: Annals of the rheumatic diseases, (1989 Aug) 48 (8) 677-82. Journal code: 0372355. ISSN: 0003-4967.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19891020

L19 ANSWER 7 OF 7 MEDLINE on STN
ACCESSION NUMBER: 85003720 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6479199
TITLE: Association of circulating immune complexes with glomerular proteinuria in patients with transitional cell carcinoma of the urinary bladder.
AUTHOR: Skaarup P; Jensenius J C; Brandslund I; Svehag S E; Wolf H
SOURCE: European urology, (1984) 10 (4) 249-53. Journal code: 7512719. ISSN: 0302-2838.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198411
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19841101

=> d kwic 1

L19 ANSWER 1 OF 7 MEDLINE on STN
AB To overcome rapid diffusion and **clearance** from the implant site and to **increase** stability, recombinant transforming growth factor beta2 (TGF-beta2) was covalently bound to injectable bovine dermal fibrillar collagen (FC) and its activity. . . to admixed TGF-beta2. Covalent binding was achieved in a two-step procedure: First, TGF-beta2 was reacted with the difunctional polyethylene glycol (**PEG**) linker, and then the **PEG**-attached TGF-beta2 (**PEG** -TGF-beta2) was bound to the fibrillar collagen (FC-**PEG** -TGF-beta2). Initial binding of TGF-beta2 to difunctional succinimidyl glutarate (D-SG-**PEG**) or succinimidyl propionate polyethylene glycol (D-SE-**PEG**) linkers was completed after reacting for 8 or 10 min as monitored by reverse-phase high-performance liquid chromatography. After reaction with injectable fibrillar collagen, extraction of unbound **PEG**-TGF-beta2 and Western blot analysis, using a TGF-beta specific **antibody**, demonstrated that at least 85% of the TGF-beta2 was bound to the fibrillar collagen. The activity of **PEG**-TGF-beta2 was fully stable in phosphate-buffered saline at 4 degrees C and 37 degrees C for at least up to 4. . . inactivated after 1 week of incubation, as measured by the mink lung epithelial cell (Mv1Lu) growth inhibition assay. Formulations of FC-**PEG**-TGF-beta2 containing 40 microg/ mL TGF-beta2 were implanted subcutaneously into rats and analyzed after days 7, 21, and 42. All TGF-beta2-containing. . . the TGF-beta typical fibroblastic response at the day 7 time point. Covalent binding of TGF-beta2 to collagen with both difunctional **PEG** crosslinkers resulted in a significantly stronger and longer-lasting TGF-beta2 response than that observed with admixed formulations of collagen and TGF-beta. The TGF-beta response with FC-**PEG**-TGF-beta2 lasted up to day 42 but was not seen after day 7 for TGF-beta2 admixed to FC. These findings clearly demonstrate that TGF-beta2 remains fully active after being covalently bound to collagen via difunctional **PEG**. In addition, covalent binding potentiates and prolongs in vivo TGF-beta responses and stabilizes the TGF-beta in vitro. Results suggest that. . .

=> d kwic 2

L19 ANSWER 2 OF 7 MEDLINE on STN
TI Immunogenicity and pharmacokinetic attributes of **poly**(**ethylene glycol**)-grafted immunoliposomes.
AB Immunoliposomes composed of hydrogenated soy phosphatidylcholine, cholesterol, **methoxypoly**(**ethylene glycol**)-distearoyl phosphatidylethanolamine (mPEG-DSPE), and hydrazide-**PEG**-DSPE (mole ratio, 57:38:3.3:1.7) linked to periodate-oxidized chimerized mouse IgG (C225, anti-human epidermal growth factor receptor) were prepared by an optimized. . . (MRT = 8.5 h, Cl = 0.2 ml/h). Subsequent injections of the immunoliposomes into the same animals resulted in rapid **clearance** (MRT < or = 0.7 h, Cl > or = 7 ml/h), which was accompanied by a significant **increase** in anti-C225 specific titers. Upon repeated injection or coinjection with the parent liposomes free C225 consistently exhibited prolonged circulation without any **increase** in C225-specific antisera, but was cleared quickly when administered into animals that had been pretreated with the immunoliposomes. Screening of. . . the immune response was specifically triggered by the constant human region of C225. These results demonstrate that the preparations of **PEG**-grafted immunoliposomes are more immunogenic than the free IgG component, which is of profound importance to the **antibody**-mediated liposomal drug delivery effort.
CT Check Tags: Male

Animals
Antibodies, Monoclonal: AD, administration & dosage
Antibodies, Monoclonal: IM, immunology
*Drug Delivery Systems
Enzyme-Linked Immunosorbent Assay
Flow Cytometry
Humans
Immunoglobulins, Fab: ME, metabolism
*Liposomes: IM, immunology
. . .
CN 0 (**Antibodies**, Monoclonal); 0 (Immunoglobulins, Fab); 0 (Liposomes); 0 (Phosphatidylethanolamines); 0 (Polyethylene Glycols); EC 2.7.1.112 (Receptor, Epidermal Growth Factor)

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 9.14 16.22

FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 23 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 22 Aug 2005 (20050822/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s PEG
33003 PEG
1125 PEGS
L20 33476 PEG
(PEG OR PEGS)

=> s poly () ethylene () glycol
644812 POLY
2 POLIES
644813 POLY
(POLY OR POLIES)
506522 ETHYLENE
3337 ETHYLENES
507988 ETHYLENE
(ETHYLENE OR ETHYLENES)
334892 GLYCOL
44021 GLYCOLS
349919 GLYCOL
(GLYCOL OR GLYCOLS)

```
L21      12996 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol
           228 METHOXYPOLY
        506522 ETHYLENE
          3337 ETHYLENES
        507988 ETHYLENE
                 (ETHYLENE OR ETHYLENES)
        334892 GLYCOL
         44021 GLYCOLS
        349919 GLYCOL
                 (GLYCOL OR GLYCOLS)
        122310 ETHYLENE GLYCOL
                 (ETHYLENE(W)GLYCOL)
L22        144 METHOXYPOLY (W) ETHYLENE GLYCOL

=> s l22 or l21 or l20
L23      41717 L22 OR L21 OR L20

=> s antibod?
L24     440322 ANTIBOD?

=> s clearance or clear or excret? or removed or removal
         67750 CLEARANCE
          5064 CLEARANCES
         69883 CLEARANCE
                 (CLEARANCE OR CLEARANCES)
        191308 CLEAR
           942 CLEARS
        192117 CLEAR
                 (CLEAR OR CLEARS)
        158408 EXCRET?
        390380 REMOVED
        620820 REMOVAL
          5047 REMOVALS
        622011 REMOVAL
                 (REMOVAL OR REMOVALS)
L25    1304988 CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL

=> s clearance or clear? or excret? or removed or removal
         67750 CLEARANCE
          5064 CLEARANCES
         69883 CLEARANCE
                 (CLEARANCE OR CLEARANCES)
        422339 CLEAR?
        158408 EXCRET?
        390380 REMOVED
        620820 REMOVAL
          5047 REMOVALS
        622011 REMOVAL
                 (REMOVAL OR REMOVALS)
L26    1459976 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL

=> s increase? or accelerat?
       3483178 INCREASE?
        330235 ACCELERAT?
L27    3736368 INCREASE? OR ACCELERAT?
 75% OF LIMIT FOR TOTAL ANSWERS REACHED

=> s l26 (S) l27
L28      99738 L26 (S) L27

=> s l24 and l28
```

```
L29       1750 L24 AND L28

=> s l29 and l23
L30         16 L29 AND L23

=> s anti-PEG
        378223 ANTI
             9 ANTIS
        378230 ANTI
                 (ANTI OR ANTIS)
         33003 PEG
          1125 PEGS
         33476 PEG
                 (PEG OR PEGS)
L31          9 ANTI-PEG
                 (ANTI(W)PEG)

=> s l31 not py>1999
       5788970 PY>1999
L32          3 L31 NOT PY>1999

=> d ibib 1-3

L32  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1999:239090  CAPLUS
DOCUMENT NUMBER:          131:63325
TITLE:                    Accelerated Clearance of Polyethylene Glycol-Modified
                          Proteins by Anti-Polyethylene Glycol IgM
AUTHOR(S):                Cheng, Tian-Lu; Wu, Pin-Yi; Wu, Ming-Fang; Chern,
                          Ji-Wang; Roffler, Steve R.
CORPORATE SOURCE:         Institute of Biomedical Sciences, Academia Sinica,
                          Taipei, Taiwan
SOURCE:                   Bioconjugate Chemistry (1999), 10(3), 520-528
                          CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          48    THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1998:24552  CAPLUS
DOCUMENT NUMBER:          128:162592
TITLE:                    Immobilization of L-asparaginase into a biocompatible
                          poly(ethylene glycol)-albumin hydrogel: evaluation of
                          performance in vivo
AUTHOR(S):                Jean-Francois, Jacques; D'urso, Edith Marie; Fortier,
                          Guy
CORPORATE SOURCE:         Laboratoire d'Enzymologie Appliquee, Departement de
                          Chimie-Biochimie, Universite du Quebec, Montreal,
                          Montreal, QC, H3C 3P8, Can.
SOURCE:                   Biotechnology and Applied Biochemistry (1997), 26(3),
                          203-212
                          CODEN: BABIEC; ISSN: 0885-4513
PUBLISHER:                Portland Press Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          46    THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32  ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1983:15249  CAPLUS
DOCUMENT NUMBER:          98:15249
```

```
TITLE:                  Antibodies against polyethylene glycol produced in
                        animals by immunization with monomethoxy polyethylene
                        glycol-modified proteins
AUTHOR(S):              Richter, Ary Wolfgang; Aakerblom, Eva
CORPORATE SOURCE:       Dep. Biomed. Res., Pharm. AB, Uppsala, 75104, Swed.
SOURCE:                 International Archives of Allergy and Applied
                        Immunology (1983), 70(2), 124-31
                        CODEN: IAAAAM; ISSN: 0020-5915
DOCUMENT TYPE:          Journal
LANGUAGE:               English


=> d his

     (FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
               E "PEG"/CN 25
L1             1 S E3

     FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2           185 S L1
L3          9685 S PEG
L4          2487 S POLY () ETHYLENE () GLYCOL
L5            52 S METHOXYPOLY () ETHYLENE GLYCOL
L6         10866 S L5 OR L4 OR L3
L7        694206 S ANTIBOD?
L8        538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9          1041 S L8 AND L6
L10          129 S L9 AND L7
L11            7 S ANTI-PEG
L12            2 S L11 AND L8
L13            3 S L11 NOT PY>1999
L14           97 S L10 NOT PY>1999
L15           90 S L14 NOT PY>1998
L16      1898836 S INCREASE? OR ACCELERAT?
L17           24 S L16 AND L15
L18        51664 S L16 (S) L8
L19            7 S L18 AND L17

     FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005
L20        33476 S PEG
L21        12996 S POLY () ETHYLENE () GLYCOL
L22          144 S METHOXYPOLY () ETHYLENE GLYCOL
L23        41717 S L22 OR L21 OR L20
L24       440322 S ANTIBOD?
L25      1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L26      1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L27      3736368 S INCREASE? OR ACCELERAT?
L28        99738 S L26 (S) L27
L29         1750 S L24 AND L28
L30           16 S L29 AND L23
L31            9 S ANTI-PEG
L32            3 S L31 NOT PY>1999

=> s l30 not py>1998
       6611305 PY>1998
L33            6 L30 NOT PY>1998

=> d ibib 1-3

L33  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1998:90995  CAPLUS
```

DOCUMENT NUMBER: 128:196557
TITLE: Improved local delivery of TGF-β2 by binding to injectable fibrillar collagen via difunctional polyethylene glycol
AUTHOR(S): Bentz, H.; Schroeder, J. A.; Estridge, T. D.
CORPORATE SOURCE: Research and Development, Collagen Corporation, Palo Alto, CA, 94303, USA
SOURCE: Journal of Biomedical Materials Research (1998), 39(4), 539-548
CODEN: JBMRBG; ISSN: 0021-9304
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:463486 CAPLUS
DOCUMENT NUMBER: 127:99686
TITLE: Immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes
AUTHOR(S): Zalipsky, S.; Harding, J. A.; Engbers, C. M.; Newman, M. S.; Goldstein, N. I.
CORPORATE SOURCE: SEQUUS Pharmaceuticals, Inc., Menlo Park, CA, 94025, USA
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1997), 24th, 87-88
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

L33 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:420003 CAPLUS
DOCUMENT NUMBER: 127:140290
TITLE: Immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol**)-grafted immunoliposomes
AUTHOR(S): Harding, Jennifer A.; Engbers, Charles M.; Newman, Mary S.; Goldstein, Neil I.; Zalipsky, Samuel
CORPORATE SOURCE: SEQUUS Pharmaceuticals, Incorporated, 960 Hamilton Court, Menlo Park, USA
SOURCE: Biochimica et Biophysica Acta (1997), 1327(2), 181-192
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d kwic 2

L33 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AB Prepns. of site-specifically constructed, aggregation free **PEG** -grafted immunoliposomes are more immunogenic than free C225 **antibodies** (Ab). This immunogenicity potentiation was almost entirely due to the constant human Fc region of the Ab. Presence of C225-specific Ab's in the immunoliposome-treated rats dramatically **accelerated clearance** of subsequently injected immunoliposomes or free C225. Negligible response to the Fab portion of conjugated C225 was detected, suggesting that use of Fab' as a targeting

moiety on **PEG**-liposomes is less likely to cause immunogenicity related problems. These observations are of importance to **antibody**-mediated liposomal drug delivery.

ST immunoliposome **PEG** grafted **antibody**

IT Epidermal growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antibodies** to; immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

IT Polyoxyalkylenes, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(derivs., conjugates with C225 **antibody**; immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

IT **Antibodies**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(to EGF receptor, conjugates with **PEG** derivs.; immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

IT 25322-68-3D, **Peg**, derivs., conjugates with C225 **antibody**
171115-99-4D, derivs., conjugates with C225 **antibody**
178744-28-0D, derivs., conjugates with C225 **antibody**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(immunogenicity-pharmacokinetics relationship of polyethylene glycol-grafted immunoliposomes)

=> d kwic 3

L33 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

TI Immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes

AB Immunoliposomes composed of hydrogenated soy phosphatidylcholine, cholesterol, **methoxypoly(ethylene glycol)**-distearoyl phosphatidylethanolamine (mPEG-DSPE), and hydrazide-**PEG**-DSPE (mole ratio, 57:38:3.3:1.7) linked to periodate-oxidized chimerized mouse IgG (C225, anti-human epidermal growth factor receptor) were prepared by an optimized. . . (MRT = 8.5 h, Cl = 0.2 mL/h). Subsequent injections of the immunoliposomes into the same animals resulted in rapid **clearance** (MRT≤0.7 h, Cl≥7 mL/h), which was accompanied by a significant **increase** in anti-C225 specific titers. Upon repeated injection or coinjection with the parent liposomes free C225 consistently exhibited prolonged circulation without any **increase** in C225-specific antisera, but was **cleared** quickly when administered into animals that had been pretreated with the immunoliposomes. Screening of the immunoliposome induced antisera against human. . . the immune response was specifically triggered by the constant human region of C225. These results demonstrate that the prepns. of **PEG**-grafted immunoliposomes are more immunogenic than the free IgG component, which is of profound importance to the **antibody**-mediated liposomal drug delivery effort.

ST immunoliposome **PEG** grafted; pharmacokinetics immunoliposome **PEG** grafted

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(G; immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

IT Epidermal growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antibodies** to; immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

IT Phosphatidylcholines, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

IT Drug delivery systems
(immunoliposomes; immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

IT Polyoxyalkylenes, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction products with distearoylphosphatidylethanolamine, hydrazide derivative; immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

IT 4537-76-2DP, Distearoylphosphatidylethanolamine, reaction products with **PEG** derivs. 9004-74-4DP, Methoxypolyethylene glycol, reaction products with distearoylphosphatidylethanolamine 25322-68-3DP, **PEG**, reaction products with distearoylphosphatidylethanolamine, hydrazide derivative
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(immunogenicity and pharmacokinetic attributes of **poly(ethylene glycol)**-grafted immunoliposomes)

=> d ibib 4-6

L33 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:292108 CAPLUS
DOCUMENT NUMBER: 122:75593
TITLE: The potential for enhanced tumor localization by **poly(ethylene glycol)** modification of anti-CEA **antibody**
AUTHOR(S): Pedley, R. B.; Boden, J. A.; Boden, R.; Begent, R. H. J.; Turner, A.; Haines, A. M. R.; King, D. J.
CORPORATE SOURCE: Department Clinical Oncology, Royal Free Hospital School Medicine, London, NW3 2PF, UK
SOURCE: British Journal of Cancer (1994), 70(6), 1126-30
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

L33 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:250975 CAPLUS
DOCUMENT NUMBER: 118:250975
TITLE: Radioimmunoassay for the pyridinoline crosslinked carboxy-terminal telopeptide of type I collagen: a new serum marker of bone collagen degradation
AUTHOR(S): Risteli, Juha; Elomaa, Inkeri; Niemi, Seija; Novamo, Anne; Risteli, Leila
CORPORATE SOURCE: Dep. Med. Biochem., Univ. Oulu, Oulu, SF-90220, Finland
SOURCE: Clinical Chemistry (Washington, DC, United States) (1993), 39(4), 635-40
CODEN: CLCHAU; ISSN: 0009-9147

DOCUMENT TYPE: Journal
LANGUAGE: English

L33 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:550137 CAPLUS
DOCUMENT NUMBER: 115:150137
TITLE: Use of site-directed mutagenesis to enhance the epitope-shielding effect of covalent modification of proteins with polyethylene glycol
AUTHOR(S): Hershfield, Michael S.; Chaffee, Sara; Koro-Johnson, Lillian; Mary, Ann; Smith, Albert A.; Short, Steven A.
CORPORATE SOURCE: Med. Cent., Duke Univ., Durham, NC, 27710, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1991), 88(16), 7185-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

=> file pctfull
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 62.60 78.82

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE ENTRY TOTAL SESSION
CA SUBSCRIBER PRICE -1.46 -1.46

FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005
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FILE LAST UPDATED: 22 AUG 2005 <20050822/UP>
MOST RECENT UPDATE WEEK: 200533 <200533/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s PEG
33330 PEG
4725 PEGS
L34 35377 PEG
(PEG OR PEGS)

=> s poly () ethylene () glycol
106749 POLY
281 POLIES
107011 POLY
(POLY OR POLIES)
94414 ETHYLENE
486 ETHYLENES
94496 ETHYLENE
(ETHYLENE OR ETHYLENES)
99346 GLYCOL
38678 GLYCOLS
106001 GLYCOL
(GLYCOL OR GLYCOLS)
L35 5321 POLY (W) ETHYLENE (W) GLYCOL

=> s methoxypoly () ethylene glycol
179 METHOXYPOLY
94414 ETHYLENE
486 ETHYLENES
94496 ETHYLENE

```
                (ETHYLENE OR ETHYLENES)
         99346 GLYCOL
         38678 GLYCOLS
        106001 GLYCOL
                (GLYCOL OR GLYCOLS)
         34591 ETHYLENE GLYCOL
                (ETHYLENE(W)GLYCOL)
L36         76 METHOXYPOLY (W) ETHYLENE GLYCOL

=> s antibod?
L37      80487 ANTIBOD?

=> s clearance or clear? or excret? or removed or removal
         40394 CLEARANCE
          3516 CLEARANCES
         41825 CLEARANCE
                (CLEARANCE OR CLEARANCES)
        285091 CLEAR?
         16591 EXCRET?
        339076 REMOVED
            14 REMOVEDS
        339079 REMOVED
                (REMOVED OR REMOVEDS)
        186688 REMOVAL
           807 REMOVALS
        186876 REMOVAL
                (REMOVAL OR REMOVALS)
L38     492783 CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL

=> s increase? or accelerat?
        477801 INCREASE?
         83290 ACCELERAT?
L39     496097 INCREASE? OR ACCELERAT?

=> s l38 (S) l39
L40      83462 L38 (S) L39

=> s anti-PEG
        159836 ANTI
           158 ANTIS
        159865 ANTI
                (ANTI OR ANTIS)
         33330 PEG
          4725 PEGS
         35377 PEG
                (PEG OR PEGS)
L41          7 ANTI-PEG
                (ANTI(W)PEG)

=> s l41 and l40
L42          5 L41 AND L40

=> d ibib 1-3

L42    ANSWER 1 OF 5     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2005072385 PCTFULL  ED 20050816  EW 200532
TITLE (ENGLISH):         PITUITARY ADENYLATE CYCLASE ACTIVATING PEPTIDE (PACAP)
                         RECEPTOR (VPAC2) AGONISTS AND THEIR PHARMACOLOGICAL
                         METHODS OF USE
TITLE (FRENCH):          AGONISTES DU RECEPTEUR (VPAC2) DU TYPE PEPTIDES
                         ACTIVANT L'ADENYLATE CYCLASE HYPOPHYSAIRE (PACAP) ET
                         PROCEDES PHARMACOLOGIQUES D'UTILISATION DE CES
                         AGONISTES
```

INVENTOR(S): CLAIRMONT, Kevin, 80 Merwin Circle, Cheshire, Connecticut 06410, US [US, US];
LUMB, Kevin, J., 520 Granite Road, Guilford, Connecticut 06437, US [US, US];
BUCKHOLZ, Thomas, 10 Morehouse Avenue, Milford, Connecticut 06460, US [US, US];
SALHANICK, Arthur, I., 430 Bellevue Road, New Haven, Connecticut 06511, US [US, US]

PATENT ASSIGNEE(S): BAYER PHARMACEUTICALS CORPORATION, 400 Morgan Lane, West Haven, Connecticut 06516, US [US, US], for all designates States except US;
CLAIRMONT, Kevin, 80 Merwin Circle, Cheshire, Connecticut 06410, US [US, US], for US only;
LUMB, Kevin, J., 520 Granite Road, Guilford, Connecticut 06437, US [US, US], for US only;
BUCKHOLZ, Thomas, 10 Morehouse Avenue, Milford, Connecticut 06460, US [US, US], for US only;
SALHANICK, Arthur, I., 430 Bellevue Road, New Haven, Connecticut 06511, US [US, US], for US only

AGENT: GREENMAN, Jeffrey, M.$, Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, Connecticut 06516$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005072385	A2	20050811

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LT LU MC NL PL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2005-US2609 A 20050127
PRIORITY INFO.: US 2004-60/539,550 20040127
US 2004-60/566,499 20040429

L42 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2005016974 PCTFULL ED 20050302 EW 200508
TITLE (ENGLISH): SIALIC ACID DERIVATIVES FOR PROTEIN DERIVATISATION AND CONJUGATION
TITLE (FRENCH): DERIVE D'ACIDE SIALIQUE DESTINE A LA DERIVATISATION ET A LA CONJUGAISON PROTEINIQUE
INVENTOR(S): JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];
HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];

PAPAOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB]

PATENT ASSIGNEE(S): LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for all designates States except US;
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB], for US only;
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;
HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;
PAPAOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only

AGENT: GILL JENNINGS & EVERY$, Broadgate House, 7 Eldon Street, London EC2M 7LH$, GB

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016974	A1	20050224

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-GB3511 A 20040812
PRIORITY INFO.: EP 2003-03254989.1 20030812

L42 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2005016973 PCTFULL ED 20050302 EW 200508
TITLE (ENGLISH): POLYSIALIC ACID DERIVATIVES
TITLE (FRENCH): DERIVES D'ACIDE POLYSIALIQUE
INVENTOR(S): HRECZUK-HIRST, Dale, Howard, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];
PAPAIOANNOU, Iaonnis, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H

9BB, GB [GR, GB]

PATENT ASSIGNEE(S): LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for all designates States except US;
HRECZUK-HIRST, Dale, Howard, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB], for US only;
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;
PAPAIOANNOU, Iaonnis, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only

AGENT: GILL JENNINGS & EVERY$, Broadgate House, 7 Eldon Street, London EC2M 7LH$, GB

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016973	A1	20050224

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-GB3488 A 20040812

PRIORITY INFO.: EP 2003-03254988.3 20030812
EP 2003-03255200.2 20030821

=> d ibib 4-5

L42 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN

ACCESSION NUMBER: 2004030617 PCTFULL ED 20040421 EW 200416

TITLE (ENGLISH): POLYMER CONJUGATES WITH DECREASED ANTIGENICITY, METHODS OF PREPARATION AND USES THEREOF

TITLE (FRENCH): CONJUGUES DE POLYMERES AVEC ANTIGENICITE REDUITE, PROCEDES DE PREPARATION ET UTILISATIONS DE CES CONJUGUES

INVENTOR(S): MARTINEZ, Alexa, L., 1944 Jonathan Avenue, San Jose, CA 95125, US;
SHERMAN, Merry, R., 1114 Royal Lane, San Carlos, CA 94070, US;
SAIFER, Mark, G., P., 1114 Royal Lane, San Carlos, CA 94070, US;
WILLIAMS, L. David, 37709 Arlene Court, Fremont, CA 94536, US

PATENT ASSIGNEE(S): MOUNTAIN VIEW PHARMACEUTICALS, INC., 3475-S Edison Way,

Menlo Park, CA 94025, US [US, US]
AGENT: GOLDSTEIN, Jorge A.$, Sterne, Kessler, Goldstein & Fox, P.L.L.C., 1100 New York Avenue, N.W., Washington, DC 20005$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004030617	A2	20040415

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-US29989 A 20030925
PRIORITY INFO.: US 2002-60/414,424 20020930
US 2002-10/317,092 20021212

L42 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2001015726 PCTFULL ED 20020828
TITLE (ENGLISH): COMPOSITIONS FOR STIMULATING CYTOKINE SECRETION AND INDUCING AN IMMUNE RESPONSE
TITLE (FRENCH): COMPOSITIONS STIMULANT LA SECRETION DE CYTOKINE ET PROVOQUANT UNE REACTION IMMUNITAIRE
INVENTOR(S): SEMPLE, Sean, C.;
HARASYM, Troy, O.;
KLIMUK, Sandra, K.;
KOJIC, Ljiljiana, D.;
BRAMSON, Jonathan, L.;
MUI, Barbara;
HOPE, Michael, J.
PATENT ASSIGNEE(S): INEX PHARMACEUTICALS CORP.;
SEMPLE, Sean, C.;
HARASYM, Troy, O.;
KLIMUK, Sandra, K.;
KOJIC, Ljiljiana, D.;
BRAMSON, Jonathan, L.;
MUI, Barbara;
HOPE, Michael, J.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001015726	A2	20010308

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-CA1013 A 20000828

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PRIORITY INFO.:         US 1999-60/151,211      19990827
                        US 2000-60/176,406      20000113


=> d his

     (FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
                E "PEG"/CN 25
L1             1 S E3

     FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2           185 S L1
L3          9685 S PEG
L4          2487 S POLY () ETHYLENE () GLYCOL
L5            52 S METHOXYPOLY () ETHYLENE GLYCOL
L6         10866 S L5 OR L4 OR L3
L7        694206 S ANTIBOD?
L8        538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9          1041 S L8 AND L6
L10          129 S L9 AND L7
L11            7 S ANTI-PEG
L12            2 S L11 AND L8
L13            3 S L11 NOT PY>1999
L14           97 S L10 NOT PY>1999
L15           90 S L14 NOT PY>1998
L16      1898836 S INCREASE? OR ACCELERAT?
L17           24 S L16 AND L15
L18        51664 S L16 (S) L8
L19            7 S L18 AND L17

     FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005
L20        33476 S PEG
L21        12996 S POLY () ETHYLENE () GLYCOL
L22          144 S METHOXYPOLY () ETHYLENE GLYCOL
L23        41717 S L22 OR L21 OR L20
L24       440322 S ANTIBOD?
L25      1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L26      1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L27      3736368 S INCREASE? OR ACCELERAT?
L28        99738 S L26 (S) L27
L29         1750 S L24 AND L28
L30           16 S L29 AND L23
L31            9 S ANTI-PEG
L32            3 S L31 NOT PY>1999
L33            6 S L30 NOT PY>1998

     FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005
L34        35377 S PEG
L35         5321 S POLY () ETHYLENE () GLYCOL
L36           76 S METHOXYPOLY () ETHYLENE GLYCOL
L37        80487 S ANTIBOD?
L38       492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L39       496097 S INCREASE? OR ACCELERAT?
L40        83462 S L38 (S) L39
L41            7 S ANTI-PEG
L42            5 S L41 AND L40

=> s l34 or l35 or l36
L43       38102 L34 OR L35 OR L36

=> s l43 (S) l37
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L44        3934 L43 (S) L37

=> s l44 and l40
L45        1413 L44 AND L40

=> s l44 (P) l40
L46        1018 L44 (P) L40

=> s anti-(polyethylene glycol)
MISSING OPERATOR 'ANTI-(POLYETHYLE'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s anti () (polyethylene glycol)
        159836 ANTI
           158 ANTIS
        159865 ANTI
                  (ANTI OR ANTIS)
        123593 POLYETHYLENE
          5298 POLYETHYLENES
        124334 POLYETHYLENE
                  (POLYETHYLENE OR POLYETHYLENES)
         99346 GLYCOL
         38678 GLYCOLS
        106001 GLYCOL
                  (GLYCOL OR GLYCOLS)
         62856 POLYETHYLENE GLYCOL
                  (POLYETHYLENE(W)GLYCOL)
L47           3 ANTI (W) (POLYETHYLENE GLYCOL)

=> d ibib 1-3

L47    ANSWER 1 OF 3     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2005016974 PCTFULL  ED 20050302  EW 200508
TITLE (ENGLISH):         SIALIC ACID DERIVATIVES FOR PROTEIN DERIVATISATION AND
                         CONJUGATION
TITLE (FRENCH):          DERIVE D'ACIDE SIALIQUE DESTINE A LA DERIVATISATION ET
                         A LA CONJUGAISON PROTEINIQUE
INVENTOR(S):             JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,
                         Hamilton House, Mabledon Place, London WC1H 9BB, GB
                         [IN, GB];
                         LAING, Peter, Lipoxen Technologies Limited, Suite 303,
                         Hamilton House, Mabledon Place, London WC1H 9BB, GB
                         [GB, GB];
                         GREGORIADIS, Gregory, Lipoxen Technologies Limited,
                         Suite 303, Hamilton House, Mabledon Place, London WC1H
                         9BB, GB [CA, GB];
                         HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies
                         Limited, Suite 303, Hamilton House, Mabledon Place,
                         London WC1H 9BB, GB [GB, GB];
                         PAPAOANNOU, Yiannis, Lipoxen Technologies Limited,
                         Suite 303, Hamilton House, Mabledon Place, London WC1H
                         9BB, GB [GR, GB]
PATENT ASSIGNEE(S):      LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton
                         House, Mabledon Place, London WC1H 9BB, GB [GB, GB],
                         for all designates States except US;
                         JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303,
                         Hamilton House, Mabledon Place, London WC1H 9BB, GB
                         [IN, GB], for US only;
                         LAING, Peter, Lipoxen Technologies Limited, Suite 303,
                         Hamilton House, Mabledon Place, London WC1H 9BB, GB
                         [GB, GB], for US only;
                         GREGORIADIS, Gregory, Lipoxen Technologies Limited,
```

Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;
HRECZUK-HRIST, Dale, Howard, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;
PAPAOANNOU, Yiannis, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only

AGENT: GILL JENNINGS & EVERY$, Broadgate House, 7 Eldon Street, London EC2M 7LH$, GB

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016974	A1	20050224

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2004-GB3511 A 20040812
PRIORITY INFO.: EP 2003-03254989.1 20030812

L47 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2005016973 PCTFULL ED 20050302 EW 200508
TITLE (ENGLISH): POLYSIALIC ACID DERIVATIVES
TITLE (FRENCH): DERIVES D'ACIDE POLYSIALIQUE
INVENTOR(S): HRECZUK-HIRST, Dale, Howard, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB];
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB];
GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB];
PAPAIOANNOU, Iaonnis, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB]
PATENT ASSIGNEE(S): LIPOXEN TECHNOLOGIES LIMITED, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for all designates States except US;
HRECZUK-HIRST, Dale, Howard, Lipoxon Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;
JAIN, Sanjay, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [IN, GB], for US only;
LAING, Peter, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GB, GB], for US only;

GREGORIADIS, Gregory, Lipoxen Technologies Limited, Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [CA, GB], for US only;
PAPAIOANNOU, Iaonnis, Lipoxon Technologies Limited; Suite 303, Hamilton House, Mabledon Place, London WC1H 9BB, GB [GR, GB], for US only

AGENT: GILL JENNINGS & EVERY$, Broadgate House, 7 Eldon Street, London EC2M 7LH$, GB

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2005016973	A1	20050224

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

RW (ARIPO): BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-GB3488 A 20040812
PRIORITY INFO.: EP 2003-03254988.3 20030812
EP 2003-03255200.2 20030821

L47 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2004022000 PCTFULL ED 20040324 EW 200412
TITLE (ENGLISH): ANTIBIOTIC MICROSPHERES FOR TREATMENT OF INFECTIONS AND OSTEOMYELITIS
TITLE (FRENCH): MICROSPHERES ANTIBIOTIQUES POUR LE TRAITEMENT D'INFECTIONS ET DE L'OSTEOMYELITE
INVENTOR(S): AMBROSE, Catherine, G., 6431 Fannin, Houston, TX 77030, US [US, US];
CLYBURN, Terry, A, 6431 Fannin, Houston, TX 77030, US [US, US];
MIKOS, Antonios, G., P.O. Box 1892, Houston, TX 77251, US [US, US]
PATENT ASSIGNEE(S): AMBROSE, Catherine, G., 6431 Fannin, Houston, TX 77030, US [US, US];
CLYBURN, Terry, A, 6431 Fannin, Houston, TX 77030, US [US, US];
MIKOS, Antonios, G., P.O. Box 1892, Houston, TX 77251, US [US, US]
AGENT: RODDY, Kenneth, A.$, Suite 100, 2916 West T.C. Jester, Houston, TX 77018$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004022000	A2	20040318

DESIGNATED STATES

W: AE AG AL AU BA BB BR BZ CA CN CO CR CU DM DZ EC GD GE HR ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX NI NO NZ OM PG PH PL SC SG SY TN TT UA UZ VC VN YU ZA

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

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       RW (EAPO):       AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):        AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
                        MC NL PT RO SE SI SK TR
       RW (OAPI):       BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:      WO 2003-US28010      A  20030905
PRIORITY INFO.:         US 2002-60/408,496       20020905
                        US 2002-60/408,502       20020905


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     (FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
               E "PEG"/CN 25
L1             1 S E3

     FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2           185 S L1
L3          9685 S PEG
L4          2487 S POLY () ETHYLENE () GLYCOL
L5            52 S METHOXYPOLY () ETHYLENE GLYCOL
L6         10866 S L5 OR L4 OR L3
L7        694206 S ANTIBOD?
L8        538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9          1041 S L8 AND L6
L10          129 S L9 AND L7
L11            7 S ANTI-PEG
L12            2 S L11 AND L8
L13            3 S L11 NOT PY>1999
L14           97 S L10 NOT PY>1999
L15           90 S L14 NOT PY>1998
L16     1898836 S INCREASE? OR ACCELERAT?
L17           24 S L16 AND L15
L18        51664 S L16 (S) L8
L19            7 S L18 AND L17

     FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005
L20        33476 S PEG
L21        12996 S POLY () ETHYLENE () GLYCOL
L22          144 S METHOXYPOLY () ETHYLENE GLYCOL
L23        41717 S L22 OR L21 OR L20
L24       440322 S ANTIBOD?
L25      1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L26      1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L27      3736368 S INCREASE? OR ACCELERAT?
L28        99738 S L26 (S) L27
L29         1750 S L24 AND L28
L30           16 S L29 AND L23
L31            9 S ANTI-PEG
L32            3 S L31 NOT PY>1999
L33            6 S L30 NOT PY>1998

     FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005
L34        35377 S PEG
L35         5321 S POLY () ETHYLENE () GLYCOL
L36           76 S METHOXYPOLY () ETHYLENE GLYCOL
L37        80487 S ANTIBOD?
L38       492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L39       496097 S INCREASE? OR ACCELERAT?
L40        83462 S L38 (S) L39
L41            7 S ANTI-PEG
L42            5 S L41 AND L40
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L43       38102 S L34 OR L35 OR L36
L44        3934 S L43 (S) L37
L45        1413 S L44 AND L40
L46        1018 S L44 (P) L40
L47           3 S ANTI () (POLYETHYLENE GLYCOL)

=> s l46 not py>1999
        581472 PY>1999
L48         282 L46 NOT PY>1999

=> s l43/ab
            662 PEG/AB
            227 PEGS/AB
            831 PEG/AB
                  ((PEG OR PEGS)/AB)
           3882 POLY/AB
            132 POLIES/AB
           4014 POLY/AB
                  ((POLY OR POLIES)/AB)
           6371 ETHYLENE/AB
             22 ETHYLENES/AB
           6377 ETHYLENE/AB
                  ((ETHYLENE OR ETHYLENES)/AB)
           3431 GLYCOL/AB
            453 GLYCOLS/AB
           3707 GLYCOL/AB
                  ((GLYCOL OR GLYCOLS)/AB)
            122 POLY/AB (W) ETHYLENE/AB (W) GLYCOL/AB
              0 METHOXYPOLY/AB
           6371 ETHYLENE/AB
             22 ETHYLENES/AB
           6377 ETHYLENE/AB
                  ((ETHYLENE OR ETHYLENES)/AB)
           3431 GLYCOL/AB
            453 GLYCOLS/AB
           3707 GLYCOL/AB
                  ((GLYCOL OR GLYCOLS)/AB)
            604 ETHYLENE GLYCOL/AB
                  ((ETHYLENE(W)GLYCOL)/AB)
              0 METHOXYPOLY/AB (W) ETHYLENE GLYCOL/AB
L49         930 ((PEG/AB) OR (POLY/AB (W) ETHYLENE/AB (W) GLYCOL/AB) OR (METHOXY
                POLY/AB (W) ETHYLENE GLYCOL/AB))

=> s l49 and l48
L50          12 L49 AND L48

=> s l50 not py>1998
        649032 PY>1998
L51          11 L50 NOT PY>1998

=> d ibib 1-5

L51    ANSWER 1 OF 11    PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        1998048837 PCTFULL  ED 20020514
TITLE (ENGLISH):         POLYALKYLENE OXIDE-MODIFIED SINGLE CHAIN POLYPEPTIDES
TITLE (FRENCH):          POLYPEPTIDES A CHAINE UNIQUE MODIFIES PAR OXYDE DE
                         POLYALKYLENE
INVENTOR(S):             WHITLOW, Marc;
                         SHORR, Robert, G., L.;
                         FILPULA, David, R.;
                         LEE, Lihsyng, S.
PATENT ASSIGNEE(S):      ENZON, INC.
LANGUAGE OF PUBL.:       English
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DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9848837	A1	19981105

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US8654 A 19980430
PRIORITY INFO.: US 1997-60/044,449 19970430
US 1997-60/050,472 19970623
US 1997-60/063,074 19971027
US 1997-60/067,341 19971202

L51 ANSWER 2 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1998044143 PCTFULL ED 20020514
TITLE (ENGLISH): POLYMER-MODIFIED VIRUSES
TITLE (FRENCH): VIRUS MODIFIES PAR DES POLYMERES
INVENTOR(S): SMITH, Alan, E.;
O'RIORDAN, Catherine, R.;
FRANCIS, Gillian, E.;
PARKES, Vincent;
DELGADO, Christina
PATENT ASSIGNEE(S): GENZYME CORPORATION;
POLYMASC PHARMACEUTICAL, PLC;
SMITH, Alan, E.;
O'RIORDAN, Catherine, R.;
FRANCIS, Gillian, E.;
PARKES, Vincent;
DELGADO, Christina
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9844143	A1	19981008

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US6609 A 19980403
PRIORITY INFO.: GB 1997-9706735.9 19970403
GB 1997-9719625.7 19970915
GB 1997-9722316.8 19971022

L51 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1997010847 PCTFULL ED 20020514
TITLE (ENGLISH): TARGETING OF CONJUGATES OF POLY(ETHYLENE GLYCOL) AND ANTIBODIES AGAINST GLUTAMIC ACID DECARBOXYLASE TO ISLET CELLS
TITLE (FRENCH): CIBLAGE DE CONJUGUES DE POLY(ETHYLENE GLYCOL) ET D'ANTICORPS CONTRE L'ACIDE GLUTAMIQUE DECARBOXYLASE SUR DES CELLULES INSULAIRES
INVENTOR(S): JACOBS, Harvey;

KIM, Sung, Wan;
MENARD, Virginie
PATENT ASSIGNEE(S): UNIVERSITY OF UTAH RESEARCH FOUNDATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9710847	A1	19970327

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-US15219 A 19960920
PRIORITY INFO.: US 1995-60/004,109 19950921

L51 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1997003092 PCTFULL ED 20020514
TITLE (ENGLISH): A PROCESS FOR REMOVAL OF POLYETHYLENE GLYCOL FROM A PROTEIN OR PEPTIDE SOLUTION
TITLE (FRENCH): PROCEDE POUR ELIMINER LE POLYETHYLENEGLYCOL D'UNE SOLUTION DE PROTEINES OU DE PEPTIDES
INVENTOR(S): KAERSGAARD, Per;
CARLSEN, Soren, Knud
PATENT ASSIGNEE(S): HEMASURE A/S;
KAERSGAARD, Per;
CARLSEN, Soren, Knud
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9703092	A1	19970130

DESIGNATED STATES
W: JP US AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1996-DK314 A 19960710
PRIORITY INFO.: DK 1995-823/95 19950713
DK 1995-970/95 19950904

L51 ANSWER 5 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1996034015 PCTFULL ED 20020514
TITLE (ENGLISH): MODIFIED ANTI-ICAM-1 ANTIBODIES AND THEIR USE IN THE TREATMENT OF INFLAMMATION
TITLE (FRENCH): ANTICORPS ANTI-ICAM-1 MODIFIES ET LEUR UTILISATION DANS LE TRAITEMENT DES INFLAMMATIONS
INVENTOR(S): FAANES, Ronald, B.;
MC GOFF, Paul, E.;
SHIRLEY, Bret, A.;
SCHER, David, S.
PATENT ASSIGNEE(S): BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.;
FAANES, Ronald, B.;
MC GOFF, Paul, E.;
SHIRLEY, Bret, A.;
SCHER, David, S.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE

	WO 9634015	A1 19961031
DESIGNATED STATES		
W:	AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG	
APPLICATION INFO.:	WO 1996-US5550	A 19960423
PRIORITY INFO.:	US 1995-8/427,355	19950424

=> d kwic 4

L51 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN

ABEN Polyethylene is used for fractional precipitation of proteins and peptides. Protein and peptide fractions obtained by the **PEG** fractionation methods generally contains residual **PEG**. The invention relates to a process for removing contaminating **PEG** from a solution of proteins or peptides, which process comprises adsorption of **PEG** in the protein or peptide solution to activated carbon.

ABFR . . . fractionnaire des proteines et des peptides. Les fractions de proteines et de peptides obtenues selon les methodes de fractionnement par **PEG** contiennent generalement des residus de **PEG**. La presente invention concerne un procede permettant d'eliminer d'une solution de proteines ou de peptides le **PEG** contaminant, lequel procede consiste a adsorber le **PEG** contenu dans la solution sur un carbone active.

DETD . . . application having publication number 123,375 describes manufacturing of a dry y-globulin preparation capable of intravenous injection by fractionating human plasma 5 with **PEG**. The method provides a y-globulin preparation with improved water solubility and stability against increase of anticomplementary activity and decrease of **antibody** titer.

In one aspect of this invention, the activated carbon is added to the PEG-containing protein or peptide solution batchwise, and after. . . PEG, the activated carbon is separated from the solution by methods known per se such as centrifugation, sedimitation, or filtration. The **removed** activated carbon may subsequently be washed and the washing solution may be added to the purified, more protein or peptide containing solution, to **increase** the recovery of, for example, a valuable protein or peptide in the purified solution.

. . . carbon filter with a flow rate that permits the adsorbtion of the PEG to the activated carbon in the filter. The **removal** of the PEG by filtration may be 10 combined with the **removal** of other contaminating substances, with a decolorization, or with a clarification of the solution by the activated carbon filter. The filtration. . . may subsequently be washed and the washing solution may be added to the purified more protein or peptide containing

solution, to
15 **increase** the recovery of e.g. a valuable protein or peptide
in the treated solution.

=> d kwic 3

L51 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ABEN . . . coupled to a nonimmunogenic hydrophilic polymer that provides a hydration
shell around the monoclonal antibody for inhibiting immune recognition thereof. **Poly(ethylene glycol)** is a preferred polymer. A method of reducing insulitis in an IDDM patient and a composition
therefor are also described.
ABFR . . . non immunogene
qui forme une enveloppe d'hydratation autour de l'anticorps monoclonal en vue d'inhiber la
reconnaissance immune de celui-ci. Le **poly(ethylene glycol)** est un polymere prefere. L'invention se
rapporte egalement a un procede de reduction de l'insulite chez un patient atteint d'IDDM,. . .

DETD TARGETING OF CONJUGATES OF **POLY(ETHYLENE GLYCOL)** AND **ANTIBODIES** AGAINST
GLUTAMIC ACID DECARBOXYLASE TO ISLET CELLS 11
CROSS-REFERENCE TO RELATED APPLICATIONS
This application claims the benefit of U.S.

From an immunotherapeutic approach, overt early
stage diabetes has been treated by blocking the
activating receptors on T cells with monoclonal
antibodies. In one such study, anti-lymphocyte serum
(ALS) and **antibodies** directed against CD4 and Cd8 T cell
receptors were administered to diabetic mice. T. Maki
et al., Long-term Abrogation of Autoimmune Diabetes. . . within 30 days after
treatment and lasted for about 200 days. Several
significant points about the autoimmunity of diabetes
were observed. The lymphocytic **antibodies** were
responsible for termination of the immune response,
thereby allowing islet recovery. Also, if **antibody**
BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS
FIG. 1 shows the reactions for coupling methoxy-
PEG-amine to an F(abl) fragment with a
heterobifunctional crosslinker.

Preferably, the polymer is a **poly (ethylene glycol)** ,
and more preferably has a molecular weight in the range
of about 200 to 8,000, although higher molecular weight
polymers, branched polymers, star molecules, and **PEG**
block copolymers are also within the scope of the
invention. Methoxy-**PEG** is a particularly preferred
polymer. It is also preferred that the monoclonal
antibody or fragment thereof is an F (ab I) fragment.

In the present invention, anti-GAD monoclonal
antibodies (Mab) are modified to maintain binding to
their cognate antigens while further preventing
recognition by other aspects of the immune system. In
an illustrative embodiment, the anti-GAD **antibody** is
modified by digestion with a protease and chemical

reduction with a reducing agent to yield F(ab')
fragments, which are then conjugated with various
poly(ethylene glycol) polymers (
PEG). The F(ab')
fragment retains the antigen-specific Fab binding
fragment, while the immune and complement activating Fc
fragment is removed. In addition, the poly(
ethylene
glycol) moiety provides an increased hydration
sphere
and dynamic mobility that prevents protein and cellular
interaction. Thus, the present anti-GAD-F(ab')-PEG
composition simultaneously binds GAD and prevents or
inhibits further recognition by the immune system.

Antibodies administered to experimental animals and
hydrophilic surfaces, due to the hydrating effect of
PEG. More importantly, protein (albumin and other
plasma proteins) adsorption was greatly reduced,
resulting from the high chain motility, hydration
sphere, and protein exclusion properties of PEG.

. . .
pH 7.3) and then incubated
in 250 Al of blocking buffer for 1 hour at 370C. After
incubation, the blocking buffer was removed and the
Immunol. 98-104 (1978), hereby incorporated by
reference. To further increase the immune reactivity of
the F(ab') fragment, poly(ethylene glycol) (PEG) is
conjugated to the F(abl) molecule. PEG is a linear or
branched, neutral. . .

. . .
ascites fluid was
microplate was dried. Duplicate dilutions (50 141) of
samples containing anti-GAD (IgG, F (ab') , or F (abl) -PEG)
(serum or dilutions of chromatographic fractions) were
placed in the wells and incubated for 2 hours at 370C,
followed by 3 washes with. . . microplate autoreader (EL311,
is Bio-Tek Instruments) . These values were compared to
standard curves prepared with known anti-GAD
concentrations to extrapolate the anti-GAD antibody
concentration.

. . .
either Example 1 or Example 2 was
enzymatically digested and then chemically reduced to
obtain F(abl) fragments, which could then be coupled to
PEG. The rationale behind this procedure is to obtain
an antibody fragment capable of binding to the GAD
antigen yet which lacks the Fc domain, and is conjugated
with PEG to further decrease protein and cellular
interactions.

It was anticipated that the antibodies isolated
during the previous procedures were a mixture of anti-
GAD and indigenous mouse antibodies. As a final
antigenicity of foreign immunogenic proteins and
enzymes. Therefore, PEGs of various molecular weights
are coupled to the F(ab') fragments through the
sulfhydryl groups thereof. These anti-GAD-F(ab')-PEG
compositions maintain ability to bind to islet/beta
cells while the PEG moiety masks the remainder of the
F(ab') molecule from eliciting additional immunological
events.

Example 8
Coupling of Anti-GAD-F(abl) to Activated **PEG**
In this example, a **PEG** intermediate prepared
according to the procedure of Examples 4, 6, or 7 is
Example 5
Activation of Diamino-**PEG**
For cell staining and whole body perfusion
(pharmacokinetic) evaluations, it is useful to label
anti-GAD-F(abl)-**PEG** with, for example, a radioactive or
fluorescent label. In vivo therapeutic applications of
the anti-GAD-F(abl)-**PEG** generally do not require such
labels. Current methods of labeling **antibodies** involve
forming conjugates through amine groups (fluorescent or
125I labels) or through oxidation of tyrosine residues
(125, label) These labeling methods can interfere with
antibody binding through reaction with the active site
of the **antibody**. Therefore, this example shows coupling
of the label to the **PEG** moiety. The labeled **PEG**
moiety
is later coupled to the F (ab I) fragment. This procedure
assures that labeled and unlabeled compositions have
similar affinities for. . .

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     (FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
                E "PEG"/CN 25
L1             1 S E3

     FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2           185 S L1
L3          9685 S PEG
L4          2487 S POLY () ETHYLENE () GLYCOL
L5            52 S METHOXYPOLY () ETHYLENE GLYCOL
L6         10866 S L5 OR L4 OR L3
L7        694206 S ANTIBOD?
L8        538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9          1041 S L8 AND L6
L10          129 S L9 AND L7
L11            7 S ANTI-PEG
L12            2 S L11 AND L8
L13            3 S L11 NOT PY>1999
L14           97 S L10 NOT PY>1999
L15           90 S L14 NOT PY>1998
L16      1898836 S INCREASE? OR ACCELERAT?
L17           24 S L16 AND L15
L18        51664 S L16 (S) L8
L19            7 S L18 AND L17

     FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005
L20        33476 S PEG
L21        12996 S POLY () ETHYLENE () GLYCOL
L22          144 S METHOXYPOLY () ETHYLENE GLYCOL
L23        41717 S L22 OR L21 OR L20
L24       440322 S ANTIBOD?
L25      1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L26      1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L27      3736368 S INCREASE? OR ACCELERAT?
L28        99738 S L26 (S) L27
L29         1750 S L24 AND L28
```

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L30          16 S L29 AND L23
L31           9 S ANTI-PEG
L32           3 S L31 NOT PY>1999
L33           6 S L30 NOT PY>1998

     FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005
L34       35377 S PEG
L35        5321 S POLY () ETHYLENE () GLYCOL
L36          76 S METHOXYPOLY () ETHYLENE GLYCOL
L37       80487 S ANTIBOD?
L38      492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L39      496097 S INCREASE? OR ACCELERAT?
L40       83462 S L38 (S) L39
L41           7 S ANTI-PEG
L42           5 S L41 AND L40
L43       38102 S L34 OR L35 OR L36
L44        3934 S L43 (S) L37
L45        1413 S L44 AND L40
L46        1018 S L44 (P) L40
L47           3 S ANTI () (POLYETHYLENE GLYCOL)
L48         282 S L46 NOT PY>1999
L49         930 S L43/AB
L50          12 S L49 AND L48
L51          11 S L50 NOT PY>1998

=> d ibib 6-10

L51    ANSWER 6 OF 11    PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        1994029370 PCTFULL  ED 20020513
TITLE (ENGLISH):         FACTOR IX - POLYMERIC CONJUGATES
TITLE (FRENCH):          CONJUGUES POLYMERES MODIFIANT L'ACTIVITE DU FACTEUR IX
INVENTOR(S):             HALLAHAN, Terrence, W.;
                         GILBERT, Carl, W.
PATENT ASSIGNEE(S):      ENZON, INC.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 9429370            A1 19941222
DESIGNATED STATES
       W:                AU BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL PT
                         RO RU SE SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC
                         NL PT SE
APPLICATION INFO.:       WO 1994-US6388       A  19940607
PRIORITY INFO.:          US 1993-8/073,531       19930608

L51    ANSWER 7 OF 11    PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        1994022429 PCTFULL  ED 20020513
TITLE (ENGLISH):         SOLID-TUMOR TREATMENT METHOD
TITLE (FRENCH):          PROCEDE DE TRAITEMENT D'UNE TUMEUR SOLIDE
INVENTOR(S):             ALLEN, Theresa, M.;
                         MARTIN, Francis, J.;
                         WOODLE, Martin, C.;
                         ZALIPSKY, Samuel
PATENT ASSIGNEE(S):      LIPOSOME TECHNOLOGY, INC.;
                         ALLEN, Theresa, M.;
                         MARTIN, Francis, J.;
                         WOODLE, Martin, C.;
                         ZALIPSKY, Samuel
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
```

	NUMBER	KIND	DATE
	WO 9422429	A1	19941013

DESIGNATED STATES
W: AU CA JP US AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1994-US3457 A 19940330
PRIORITY INFO.: US 1993-8/040,544 19930331

L51 ANSWER 8 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1994015625 PCTFULL ED 20020513
TITLE (ENGLISH): FACTOR VIII - POLYMERIC CONJUGATES
TITLE (FRENCH): CONJUGUES DE POLYMERE ET DE FACTEUR VIII
INVENTOR(S): HALLAHAN, Terrence, W.;
GILBERT, Carl, W.
PATENT ASSIGNEE(S): ENZON, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9415625	A1	19940721

DESIGNATED STATES
W: AU BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL PT RO RU SE SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1994-US552 A 19940113
PRIORITY INFO.: US 1993-8/003,985 19930115

L51 ANSWER 9 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1993000109 PCTFULL ED 20020513
TITLE (ENGLISH): METHOD OF STIMULATING IMMUNE RESPONSE USING GROWTH HORMONE
TITLE (FRENCH): PROCEDE DE STIMULATION DE LA REPONSE IMMUNITAIRE A L'AIDE D'HORMONE DE CROISSANCE
INVENTOR(S): CARLSSON, Lena, Mariana, Susann;
CLARK, Ross, G.;
CRONIN, Michael, J.;
JARDIEU, Paula, M.
PATENT ASSIGNEE(S): GENENTECH, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9300109	A1	19930107

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FR GB GR IT LU MC NL SE

APPLICATION INFO.: WO 1992-US4489 A 19920529
PRIORITY INFO.: US 1991-723,359 19910628

L51 ANSWER 10 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1990004606 PCTFULL ED 20020513
TITLE (ENGLISH): A PROCESS FOR FRACTIONATING POLYETHYLENE GLYCOL (PEG)-PROTEIN ADDUCTS AND AN ADDUCT OF PEG AND GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR
TITLE (FRENCH): PROCEDE DE FRACTIONNEMENT DE PRODUITS D'ADDITION DE PROTEINE-POLYETHYLENE GLYCOL (PEG) AINSI QU'UN PRODUIT D'ADDITION DE PEG ET UNFACTEUR DE STIMULATION DE COLONIES DE GRANULOCYTES-MACROPHAGES
INVENTOR(S): FISHER, Derek;
FRANCIS, Gillian, Elizabeth;
DELGADO, Cristina

PATENT ASSIGNEE(S): ROYAL FREE HOSPITAL SCHOOL OF MEDICINE;
FISHER, Derek;
FRANCIS, Gillian, Elizabeth;
DELGADO, Cristina
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9004606	A1	19900503

DESIGNATED STATES
W: AT BE CH DE FR GB IT JP LU NL SE US
APPLICATION INFO.: WO 1989-GB1261 A 19891020
PRIORITY INFO.: GB 1988-8824591.5 19881020

=> d kwic 7

L51 ANSWER 7 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ABEN . . . composition has sizes predominantly in the range 0.05 to 0.12 microns,
includes doxorubicin in entrapped form, and contains, on the **PEG** free ends, a monoclonal antibody
specific against highly proliferative cells in a lung squamous cell carcinoma.
ABFR . . . fois le temps de
circulation dans le sang desdits liposomes par rapport a celui de liposomes depourvus de cette
couche **PEG**. Des anticorps ou fragments d'anticorps (16), efficaces pour se lier specifiquement aux
antigenes associes a la tumeur, presents sur le. . .
entre 0,05 et 0,12 microns, renferme de la doxorubicine sous forme piegee, et contient, sur les
extremites libres des chaines **PEG**, un anticorps monoclonal specifiquement dirige contre des cellules
fortement proliferatives d'un epithelioma epidermoide bronchique.

DETD . . . accompanying figures and
examples,
Brief Description of the Figures
Fig* 1 illustrates a portion of a liposome in
the liposome ocomposition of the invention, having
antibodies or **antibody** fragments attached to the
free ends of polyethylene glycol (**PEG**) chains
carried on the liposome;
Fige 2 shows steps in forming a PE
derivatized by a **PEG** spacer chain having a
maleimide group at its free end;
Fige 3 illustrates the preparation of a
biotinylated PE-**PEG** for use in preparing liposomes
with **PEG**-bound biotin;
Fig. 4 shows coupling of an **antibody** to PE
derivatized with a **PEG** chain having a hydrazide
moiety at its free end;
Fig, 5 shows the coupling of an **antibody** to
PE derivatized by a **PEG** chain having a reactive
maleimide group at its free end;
Fig* 6 shows the coupling of an **antibody** to a
liposome-attached **PEG** having a hydrazide group at
its free end;
Fig* 7 is a plot of drug residence time in
the blood, expressed in terms of percent injected
dose, as a function of hours after IV injection in

rats, for liposomes containing 67Gallium and a bound **antibody** IgG (9) or liposomes with no bound **antibody** (A);
Fig o 8 shows 125dUrd uptake in normal and tumor-bearing DBA/2 mice (3/group) 45 days after i.v. injection of 2 x 105. . .

This embodiment allows the **antibody** in the polymer layer to be positioned at a selected depth in the layer to increase or decrease the extent to which the **antibody** is buried in the polymer layer.. For example, if the **antibody** is a xenogeneic **antibody** which elicits an immunogenic-response the **antibody** is preferably buried to hide immunogenic sites while retaining the antigen recognition region accessible for binding to a target site. If the **antibody** is nonimmunogenic, the **antibody** can be localized on the outer surface coating of polyethylene glycol chains'. Functionalization of **PEG** chains for this purpose, referred to herein as a spacer chain, for attachment of an **antibody** is described below.

In another embodiment the **antibody** is a biotinylated **antibody** attached to the distal ends of liposome-attached polymer ends via a biotin-strepavidin (or biotin-avidin) linkage, In one embodiment, shown in Fig. 3, a DSPE-**PEG**-NH2 is converted to DSPE-**PEG**-biotin. To the biotin moiety on the **PEG** free ends are bound avidin or strepavidin molecules. Each avidin molecule contains four high-affinity biotin binding sites and to one or more of these sites is attached the liposome bound biotin. To one or more of the free-remaining sites can be bound a biotinylated **antibody** which is derivatized by a biotin molecule.

The liposomes are then incubated with avidin and biotinylated **antibodye**
Alternatively, a DSPE derivatized with a **PEG** chain having a hydrazide group at the chain's free end may be synthesized, as illustrated in Fig. 4* Here, a hydroxy acid derivative (IX) is prepared from **PEG** using ethyl isocyanatoacetate for partial' introduction of a urethane-linked glycine residue.
.
30-75 percent vesicle-forming lipids, 25-40 percent cholesterol, 1-20 percent polymer-derivatized lipid, and 0 10 mole percent of the lipid derivative employed for **antibody** coupling, one exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH),, DSPE-**PEG** at a molar ratio of 2:1:0,1. The composition also includes 0.05 mole percent phosphatidylethanolamine derivatized with biotin (biotin-PE). Another exemplary liposome formulation includes hydrogenated soy phosphatidylethanolamine (HSPE), cholesterol (CH), and DSPE-**PEG** at a molar ratio of 2:1:0 The composition also includes I mole percent DSPE-**PEG** derivatized with hydrazide (DSPE-**PEG**-Hz).

Alternatively, an **antibody**-lipid derivative may be first formed and then incorporated into a liposome. As an example, an **antibody** is coupled to the maleimide group of a free DSPE-**PEG** molecule. The **antibody**-coupled DSPE-**PEG** molecule is then employed to form vesicles.

Alternatively, the polymer end-functionalized group is a hydrazide group (see Figure 4 discussed above). Conveniently, the hydrazide can be coupled to the **antibody** through the carbohydrate moieties present in the **antibody**, as detailed in Figure 6 and Example 1.VIII. Briefly, **antibody** hydroxyl groups are oxidized to aldehydes by mild periodate oxidation. The oxidized protein is then added to liposomes containing DSPE-**PEG**-Hz and incubated overnight, Unbound **antibodies** are then separated from **antibody**-liposomes by gel filtration.

Ive Utility
According to an important aspect of the invention, it has been found that **antibodies** can be attached to the **PEG** chain free ends without a significant loss in the blood circulation lifetime of the liposomes. This allows the **antibody**-coated liposomes to circulate for the time necessary to reach remote tumor sites and to localiz6 at the sites through **antibody**-antigen specific interactions. As a result, a significant therapeutic enhancement in tumor treatment over long-circulating liposomes in the absence of surface attached **antibodies** is possible.

A, Therapeutic Efficacy of **Antibody**-liposome Composition in vivo
Experiments were performed to investigate the half-life in the bloodstream and the tissue biodistribution of the **antibody**]liposome composition. For these experiments liposomes containing **PEG** end-functionalized with a hydrazide group covalently linked to sheep IgG were prepared as described in Example 1.VIII.

The tissue biodistribution of liposomes containing 125I-tyraminylinulin with and without covalently attached IgG **antibodies** is shown in Table I (Example 2(I)). It can be seen that the tissue biodistribution of liposomes containing **antibody** covalently attached to the end of a **PEG** chain by a hydrazide group is very similar to those of liposomes containing nonfunctionalized **PEG** chains. Liposome biodistribution was determined for the blood, liver, spleen, lung,, heart and carcass.

Other experiments to determine the blood circulation times of **antibody**-liposomes were performed using liposomes containing surface-bound avidin and biotinylated **antibodies**. Liposomes with surface-bound **antibodies** possessed long circulation times in the bloodstream similar to that of liposomes containing **PEG** derivatized

lipids but lacking the surface-bound **antibodies**.

Twenty-four hours post-injection 34.7 ± 6.7% of
.WO 94/22429 PCTIUS94/03457
20
mAb liposomes were in the blood. This level is comparable to that of liposomes containing **PEG**, but lacking the **antibody** (37.5 ± 9.7% at 24 hours).

The results obtained indicate that liposomes containing entrapped doxorubicin, lipids derivatized with **PEG**, such as **PEG**]DSPE, and containing an **antibody** on the liposomes' outer surface (mAb-liposomal DOX) are valuable for increasing the therapeutic effectiveness of doxorubicin administration to a site in a subject.
. .
compound,
multivalent species capable of binding multiple antibodies may be administered between about 24 to 48 hours after administration of the biotinylated antibodies to **accelerate clearance** of the antibodies from the bloodstream. These multivalent species may be empty liposomes having surface-bound avidin, but not containing the liposome-entrapped compound, The empty. . .

These multivalent species serve to chase nonspecifically-bound biotinylated **antibodies** from sites in the bloodstream. After the chase, liposomes containing the therapeutic compound in liposome-entrapped form, the surface-bound anti-ligand molecules, such as,avidin, and the **PEG** layer on the liposome surface are administered.

Example 1
Preparation of DSPE-**PEG**-Maleimide and **Antibody** Coupling to DSPE-**PEG**-Maleimide
Io PreRaration of the Mono 2-nitrobenzene-sulfonamide of **PEG** bis(amine) (Compound II)
A mixture of 1.7 g (0.5 mmole) of commercially available polyethylene glycol bis(amine) and 104 mg (0.55 mmole) of 2-nitrobenzene. . .

VII. **Antibody** Coupling to the Maleimide Grou'P of **PEG**
Coupling reactions were performed by adding **antibody** solution to the liposomes (final protein concentration = 0.5 mg/ml) in phosphate buffered saline and incubating the suspension overnight at ambient temperature with. . .

VIIIo **Antibody** Coupling to the Hydrazide Group of **PEG**
A 10 mg/ml solution of IgG was prepared in 100 mM sodium acetate, 70 mM NaCl pH 5 For 1 ml of protein. . . of 0.2 M sodium periodate was added. oxidation proceeded-for 1 hour at room temperature. The periodate-treated protein was added to liposomes containing DSPE-**PEG** hydrazide and incubated overnight at 40C.

Liposomes were separated from free protein by chromatography on Sepharose CL-4B in TES-buffered saline, pH 7*4*
Example 2
Biodistribution of **Antibody**-Liposomes
The biodistribution and blood circulation lifetime of liposomes containing surface-bound **antibodies** was compared to that of liposomes lacking surface-bound **antibodies**. The **antibody**-liposomes were composed of HSPC:CH:**PEG** hydrazide, at a 2:1:0.1 molar ratio, and sheep IgG covalently linked to **PEG** chain. Liposomes lacking surface-bound antigens were liposomes composed of HSPC:CH:**PEG** at a 2:1:0.1 molar ratio and liposomes, composed of HSPC:CH:**PEG** hydrazide. The average diameter of the liposomes was between 110 and 120 nanometers. For biodistribution studies the liposomes contained 125I-tyraminylinulin in liposome-entrapped form (Example 2(I)). For blood circulation lifetime studies the liposomes contained OGallium in liposome-entrapped form, The **antibody**-liposomes were prepared as described in Example 1.VIII.

25
As shown in Table 1 the biodistribution of liposomes containing **antibody** covalently attached to the end of a **PEG** chain by a hydrazide group are very similar to those of liposomes containing 30 nonfunctionalized **PEG** chains. Liposome biodistribution was determined for the blood, liver, spleen, lung, heart and carcass.
. . .
of
either 0.2 ml phosphate-buffered saline (PBS) (untreated controls) or with 6 mg/kg of either free DOX, 6 mg/kg of DOX entrapped in HSPC:CH:**PEG**-DSPE liposomes (liposomal DOX), 6 mg/kg of DOX entrapped in HSPC:CH:**PEG**-DSPE liposomes containing attached **antibody** 174H.64 (mAb-liposomal DOX) or mAb-liposomes (11-39 Ag mAb) lacking DOX, all in 0*2 ml of sterile saline.

=> d kwic 6

L51 ANSWER 6 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ABEN Conjugates containing a substance with coagulant activity, such as recombinant Factor IX, non-antigenic polymers, such as **poly(ethylene glycol)**, are disclosed. Also disclosed are methods of forming the novel conjugates of this invention.
ABFR . . . substance presentant une activite coagulante, tels que le facteur IX de recombinaison, et des polymeres non antigeniques tels que du **poly(ethylene glycol)**; et procedes de preparation de ces nouveaux conjugues.

DETD . . . to a final concentration of 10 .mM and was allowed to sit on ice for 5 minutes, Excess periodate and sucrose were **removed** by desalting on a PD-10 column as described above. A 100 fold excess PEG-

Hydrazide was added, and the reaction proceeded. . . was added to a f
inal concentration of 5 mM and
the mixture was kept refrigerated overnight, Excess PEG
and NaCNBH4 were **removed** by GPC-HPLC using a Showdex
column equilibrated with 0,1 M sodium phosphate pH 7,5,
SDS-PAGE of the purif ied material revealed a. . . 100 mM NaCl with
10 mg/ml glycine, The sample
was aliquoted -and stored at either 40C, -700C or
lyophilized, SDS-PAGE revealed an **increased** and broad
molecular weight distribution but no sign of
contaminating native protein, Specific activities were
*determined in the presence of Factor IX def. . .

SAMPLE SPECIFIC ACTIVITY (U/mg)
Native Factor IX 47
PEG-F,IX (40C) 128
PEG-F*IX (-700C) 146
PEG-F,IX (Lyoph) 115
The various embodiments of the present
invention,, therefore, provide conjugates which retain
significant levels of Factor IX activity while having
less of a tendency to cause the formation of inhibitor
antibodies.

=> d ibib 11

L51 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1986004145 PCTFULL ED 20020507
TITLE (ENGLISH): PROTEIN MODIFICATION WITH PEG
TITLE (FRENCH): MODIFICATION DE PROTEINES AVEC PEG
INVENTOR(S): TOMASI, Thomas, B.;
ANDERSON, William, L.
PATENT ASSIGNEE(S): UNIVERSITY OF NEW MEXICO
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 8604145	A1	19860717

DESIGNATED STATES
W: DE GB JP
APPLICATION INFO.: WO 1985-US2572 A 19851231
PRIORITY INFO.: US 1984-687,811 19841231

=> d kwic 11

L51 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2005 Univentio on STN
ABEN **PEG**-modified protein molecules characterized by reduced
immunogenicity are prepared by covalent
modification of the protein with **PEG** employing an active ester
intermediate. Antibodies so modified
exhibit decreased binding capacity for Fc cell surface receptors, are
non-toxic and. . .
ABFR Des molecules de proteines modifiees par **PEG** (polyethylene
glycol) caracterisees par une
immunogenicite reduite sont preparees par modification covalente de la
proteine avec **PEG** utilisant
un intermediaire d'ester actif. Des anticorps ainsi modifies presentent
une capacite de liaison
diminuee pour des recepteurs en surface. . .

DETD PROTEIN MODIFICATION WITH **PEG**

F i eld--of

Diagnostic and therapeutic procedures of the type dependent upon immunoreaction of **antibody** with a target tissue are frequently hampered by both the immunogenicity of the reagent in clinical applications and binding to cell surface Fc receptors, Immune response to **antibodies** and other foreign proteins, characterized by both allergic phenomena and inactivation of the protein, must be countered by treatment of the protein to obviate stimulation of the host immune system, while retaining desirable protein biologic activity, In addition, it is desirable to increase **antibody** specificity by reduction or elimination of Fc binding to cell surface receptors.

. . .

result was obtained in a related study J.___T 1 nnol . hiad mm --l-le-t s., 327 (1983), wherein it was concluded that **PEG**-modification of Ig mediated with cyanuric chloride destroyed **antibody** activity.

. . .

comprises a polyethylene glycol-protein derivative, and a method for preparing the derivative in excellent yields comprising covalently modifying the protein with polyethylene glycol (**PEG**) employing an active ester intermediate. Derivatized **antibodies** are characterized by retained antigen binding activity, low binding capacity for cell surface Fc recep-torsr reduced in,munogenicity, good storage stability, and non-toxicityf'and are. . . such as tumor imaging, chemotherapy, radiotherapy, and iiiurnunohistochemical procedures. It is contemplated that a broad range of diagnostic and therapeutic proteinsr including monoclonal **antibodies** and enzymes, is modifiable by the process of the invention to provide modif ied proteins having reduced irmmunogenicity and low non-sipecif ic biological. . .

Different symbols depict experiments performed on different days with different samples of **PEG**-modified **antibody**

.

An affinity purified rabbit anti-mouse immunoglobulin reagent was modified with FITC to an F/P ratio of 3.7 Qj) A f raction TPIPTOM Qz TRE

According to the invention, immunogenicity of foreign protein, especially **antibodyt** is reduced or eliminated by covalent modification of the protein with polyethylene glycol (**PEG**), employing a **PEG** active ester intermediate. In contrast to known prior art modifications, **PEG** modification of **antibodies** according to the process of the invention provides a derivative which retains avidity for antigen, while enrlhibiting reduced immunogen-icityo A particular advantage. . . reduction in non-specific binding occurst which is believed to be attributable to inactivation of the Fc portion of theantibodymolecule. Theprocessthussubstant4.allyeliminates binding of the **antibody** to cell surface Fc receptors and promotes **antibody** concentration targeted tissue in applications such

as tumor imaging and immunohistochemical techniques.

Particular **PEG** polymers useful in the process of the invention comprise substituted or unsubstituted **PEG** polymers having molecular weights of from about 1000 to 5000f which are themselves poor immunogens, and which can be coupled to -protein using. . . biologically active and substantially non-toxic and non]immunogenic. rionomethoxypolyethylene glycol (mPEG) satisfies these criteria, and is an especially suitable modif ier , particularly for **antibody**. Covalent mPEG modification of **antibody** molecule, using the present active ester approachr is accomplished with full retention of binding activity,, and yields very predictable and reproducible modifications.

. . .

While the process is particularly useful in reducing the immunogenicity of lieterologous species proteinsr the process is also applicable to hoimologous species proteins. **Antibodies** are proteins of particular interest, as by the process of the invention, the specificity and avidity of the **antibody** molecules is retained, while non-specific binding of **antibody** molecules to cellular Fc receptor and rapid clearance of the **antibody** f rom the circulation is obviated. Drugs, toxinst fluorescents, radionuclides, or other active moieties may readily bè attached to the modified **antibody** molecule via the **PEG** substituent according to principles understood by those skilled in the art for delivery to selected tissue, especially to tumor tissue for diagnosis or therapy, ONving to the decreased non-specif ic activity of complexes comprising active moieties conjugated with **PEG**-modified **antibody** or other protein, premature dissociation of the complex is avoidedt and highly selective delivery is achieved.

. . .

brief, antisera was applied to the aff fnity column and the column was washed with 0.5 U sodium thiocyanate and tile resulting **antibody** was simultaneously desalted and concentrated using a Micro Pro di Con apparatus, (Bio 1loleculare Dynaraicso Beavertonw OR), The purified **antibody** was stored sterile at 4 degrees,

.-e.asjurement.o.f Anti-Cgnalbumin Activit

Nnt'gen binding activity of the affinity purified and chemical-Ly modified **antibodies** was determined by evaluating their ability to competitively inhibit the binding of a rabbit anti-conalbuimin-alkaline phosphatase conjugate to conalbumin-coated micAroelisa plates (Vangard, Neptune, NJ). The enzyme linked **antibody** for this assay was prepared by a modification of the method described by Avermeas (Ii-timuno. Chem.]: 43j, 1969) and to assure. . . conalbumin to 10 ug/ml in 0.05 U NaHCO3 r pH 9.6 and incubating for 18 hours at room temperature, Equal volumes of **antibody** and enzyme conjugate, at the proper dilution, were then incubated in the antigen coated plates with Characteriza-tio.ja-af. Mo4iflied.-**Antibod**

Three different measurements were used to characterize the modified **antibody**. Protein concentration was determined both by optical density measurements at 280 nm,. assuming an E % 280nm = 14 Qlatho.ds.-Immuna.l. Immunocbem.2: 343,. . . , 1 948) Protein amino groups were determined by TNBS titrations as described by Habeed (Ana_1yt.._.Bioc .,hp.m.- 1.,4: 323#, 1966) The extent of **PEG**

modif ication was also evaluated by measuring an increase in protein size. For this measurement protein size was evaluated using a 06% discontinuous. . .

Dete-rminatian-of- immunageni-ai=
Immunogenicity of rabbit **antibody** and its **PEG**
-modified
derivatives were determined by measuring the **antibody** response of Swiss mice to an intraperitoneal injection of 50 gg of the antigen (rabbit **antibody**) in PBS. The mouse **antibody**
response
was determined using a two step enzyme linked assay, In brieft several two-fold dilutions of mouse sera were incubated on a rabbit. . .

The effect of mPEG modifications, using cyanuric chloride and active ester coupling procedures on **antibody** activity is reported in Table I and II. It is evident from these results that even at low modifications there is a significant decrease in **antibody** binding activity with cyanuric chloride.
Experiments
varying the rate and form of activated **PEG** along with
experiments
varying the reaction time and temperature did not significantly improve the recovery of active **antibody**. In contrastf the use of active ester to modify **antibody** with **PEG** results
in no detectable
loss in **antibody** titer or **antibody** activity.

TABLE I
Antigen &jnding &gtjyity.of -Rat' alhimin
Mad if i ad -with ag using -the,];Xantiric Chlogigle. Procrdure
% Lysine
liodification mg **Antibody**/mg Protein % Loss of Ab Activity
1*00 0
0050 50
0*15 35
0*06 94
TABLE II
Acylty,__of. Rabbit
Anti-CQ Modi-f i-ed. with
ha, ra&=9 ;Ler- of
% Lysine
Modification mg **Antibody**/mg Protein % Loss of Ab Activity
1 0 0 0
1*0 0
1*0 0
1*0 0
100 0
1*0 0
at ion, o
EXAMPTA.-I-n-, Effectiy. ansa Qf
I..--w th__mPZQ._a lo-the-,
To verify that **antibody** was significantly modified by this procedure, all mPEG-modified **antibody** preparations werz analyzed by SDS gel electrophoresis. An eXample of one series of derivatives is shown in FIG. le Results from this experiment **clearly** show that most or all molecules in the population are modified and that the apparent molecular weight **increases** greatly
following the modification. II-. should be noted however that the -modified **antibodies** tested are a distribution of molecules

each containing different number of **PEG** molecules per **antibody**.

B. The hyperresponsiveness induced by some of the mPEG-modified rabbit **antibod**-ies in A, gap-ra, was investigated by evaluating t-he adjuvant properties of **PEG**. Swiss mice were immunized with 50 mg of rabbit immunogiobuiin in the presence O.L varying **PEG** concentrations up to 1 mg/ml **PEG** and the **antibody** response determined fifteen days later. In this experiment the **PEG** was not covalently attached to the rabbit protein.

. . .

appear to have an upper limit to the cellular fluorescence intensity whereas cells detected by the reagent that was not mPEG-modified show an **increased** fluorescence intensity (FIG. 7B)o Co It was demonstrated that the mPEG-modified reagent binds to cell surface immunoglobulin whereas the non mPEG-modified reagent exhibits. . . irtimunoglobulin was used to competitively inhibit the binding of both reagents to mouse splenocytes. The results of this experiment, shown in FIG. 8, **clearly** demonstrate that the binding of the classical fluoresce-- inated reagent (not mPEG-modified) could not be completely, inhibited by antigen whereas binding of. . .

PEG-modified **antibodies** according to the invention exhibit markedly reduced imimunogenicity, low specific binding capacity for cell surface Fc receptors, and retention of antigen-binding activity. mPEG modification of **antibodies** also essentially eliminates Fc receptor binding. Covalent modification of more than 15% of amino groups of rabbit anti-conalbumin **antibody** with mPEG completely prevented immune complexes prepared with this **antibody** from binding to the Fc receptor on the murine rLiacrophage cell linef P388,D1, Similar sensitivities are observed for mPEG- modified fluorescein labelled **antibodies** since mPEG modificationdoesnotquenchfluoresceinfluorescence. Afluorescein


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=> d his

     (FILE 'HOME' ENTERED AT 08:05:57 ON 23 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 08:06:15 ON 23 AUG 2005
                E "PEG"/CN 25
L1            1 S E3

     FILE 'MEDLINE' ENTERED AT 08:07:04 ON 23 AUG 2005
L2          185 S L1
L3         9685 S PEG
L4         2487 S POLY () ETHYLENE () GLYCOL
L5           52 S METHOXYPOLY () ETHYLENE GLYCOL
L6        10866 S L5 OR L4 OR L3
L7       694206 S ANTIBOD?
L8       538410 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L9         1041 S L8 AND L6
L10         129 S L9 AND L7
L11           7 S ANTI-PEG
L12           2 S L11 AND L8
L13           3 S L11 NOT PY>1999
L14          97 S L10 NOT PY>1999
```

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L15          90 S L14 NOT PY>1998
L16     1898836 S INCREASE? OR ACCELERAT?
L17          24 S L16 AND L15
L18       51664 S L16 (S) L8
L19           7 S L18 AND L17

     FILE 'CAPLUS' ENTERED AT 08:17:28 ON 23 AUG 2005
L20       33476 S PEG
L21       12996 S POLY () ETHYLENE () GLYCOL
L22         144 S METHOXYPOLY () ETHYLENE GLYCOL
L23       41717 S L22 OR L21 OR L20
L24      440322 S ANTIBOD?
L25     1304988 S CLEARANCE OR CLEAR OR EXCRET? OR REMOVED OR REMOVAL
L26     1459976 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L27     3736368 S INCREASE? OR ACCELERAT?
L28       99738 S L26 (S) L27
L29        1750 S L24 AND L28
L30          16 S L29 AND L23
L31           9 S ANTI-PEG
L32           3 S L31 NOT PY>1999
L33           6 S L30 NOT PY>1998

     FILE 'PCTFULL' ENTERED AT 08:22:07 ON 23 AUG 2005
L34       35377 S PEG
L35        5321 S POLY () ETHYLENE () GLYCOL
L36          76 S METHOXYPOLY () ETHYLENE GLYCOL
L37       80487 S ANTIBOD?
L38      492783 S CLEARANCE OR CLEAR? OR EXCRET? OR REMOVED OR REMOVAL
L39      496097 S INCREASE? OR ACCELERAT?
L40       83462 S L38 (S) L39
L41           7 S ANTI-PEG
L42           5 S L41 AND L40
L43       38102 S L34 OR L35 OR L36
L44        3934 S L43 (S) L37
L45        1413 S L44 AND L40
L46        1018 S L44 (P) L40
L47           3 S ANTI () (POLYETHYLENE GLYCOL)
L48         282 S L46 NOT PY>1999
L49         930 S L43/AB
L50          12 S L49 AND L48
L51          11 S L50 NOT PY>1998

=> file dissab
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               56.84     135.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                0.00      -1.46

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```
=> s anti-peg
         25082 ANTI
             9 ANTIS
         25087 ANTI
                 (ANTI OR ANTIS)
          1251 PEG
           154 PEGS
          1334 PEG
                 (PEG OR PEGS)
L52          0 ANTI-PEG
                 (ANTI(W)PEG)

=> s anti () (polyethylene glycol)
         25082 ANTI
             9 ANTIS
         25087 ANTI
                 (ANTI OR ANTIS)
          3287 POLYETHYLENE
           146 POLYETHYLENES
          3344 POLYETHYLENE
                 (POLYETHYLENE OR POLYETHYLENES)
          2420 GLYCOL
           177 GLYCOLS
          2537 GLYCOL
                 (GLYCOL OR GLYCOLS)
           930 POLYETHYLENE GLYCOL
                 (POLYETHYLENE(W)GLYCOL)
L53          0 ANTI (W) (POLYETHYLENE GLYCOL)

=> d his

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     FILE 'DISSABS' ENTERED AT 08:36:44 ON 23 AUG 2005
L52           0 S ANTI-PEG
L53           0 S ANTI () (POLYETHYLENE GLYCOL)
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